

**EXAMINING U.S. PUBLIC HEALTH PREPAREDNESS  
FOR AND RESPONSE EFFORTS TO SEASONAL  
INFLUENZA**

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**HEARING**  
BEFORE THE  
SUBCOMMITTEE ON OVERSIGHT AND  
INVESTIGATIONS  
OF THE  
COMMITTEE ON ENERGY AND  
COMMERCE  
HOUSE OF REPRESENTATIVES  
ONE HUNDRED FIFTEENTH CONGRESS  
SECOND SESSION

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<sup>1</sup> Dr. Bright did not answer submitted questions for the record by the time of printing.



## **EXAMINING U.S. PUBLIC HEALTH PREPARED- NESS FOR AND RESPONSE EFFORTS TO SEASONAL INFLUENZA**

**THURSDAY, MARCH 8, 2018**

HOUSE OF REPRESENTATIVES,  
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS,  
COMMITTEE ON ENERGY AND COMMERCE,  
*Washington, DC.*

The subcommittee met, pursuant to call, at 10:56 a.m., in room 2123, Rayburn House Office Building, Hon. Gregg Harper (chairman of the subcommittee) presiding.

Members present: Representatives Harper, Griffith, Burgess, Brooks, Collins, Walberg, Walters, Carter, Walden (ex officio), DeGette, Schakowsky, Castor, Tonko, and Ruiz.

Also present: Representative Green.

Staff present: Jennifer Barblan, Chief Counsel, Oversight and Investigations; Adam Buckalew, Professional Staff Member, Health; Karen Christian, General Counsel; Ali Fulling, Legislative Clerk, Oversight and Investigations, Digital Commerce and Consumer Protection; Ed Kim, Policy Coordinator, Health; Jennifer Sherman, Press Secretary; Alan Slobodin, Chief Investigative Counsel, Oversight and Investigations; Austin Stonebraker, Press Assistant; Natalie Turner, Counsel, Oversight and Investigations; Hamlin Wade, Special Advisor for External Affairs; Christina Calce, Minority Counsel; Christopher Knauer, Minority Oversight Staff Director; and Miles Lichtman, Minority Policy Analyst.

### **OPENING STATEMENT OF HON. GREGG HARPER, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF MISSISSIPPI**

Mr. HARPER. Good morning.

This year, like so many previous years, we have had a bad flu season. After months of record-breaking, widespread flu activity, the CDC has reported that the flu season has finally peaked. We are probably still going to see flu activity until the middle of April, so if you have the flu or flu symptoms, it certainly is important to see your doctor and stay at home.

Influenza is a leading cause of death in the United States, especially in a severe flu season. Every year, thousands of Americans die from the flu and thousands more are hospitalized from flu-related complications. Since 2010, the flu has caused between 12,000 and 56,000 deaths per year.

This year was no exception. Tragically, as of February the 24th, there have already been 114 influenza-associated pediatric deaths this season. Some of those deaths have occurred in my home State of Mississippi. Although we have enhanced our preparedness for the flu in recent years, there is still room for improvement.

The best way to prevent the flu is by getting your flu shot. Millions of Americans receive a flu shot every year to help protect them against this illness. Unfortunately, there are many Americans that do not do that. Last year, only 59 percent of children and about 43 percent of adults received flu vaccination.

Even though only a little over half of Americans typically get vaccinated, CDC estimates that flu vaccination prevented 3,000 pneumonia and influenza deaths during the 2015–2016 flu season alone. Increasing the number of Americans that get the annual flu vaccine will prevent more deaths and illnesses.

Not only can the flu vaccine help prevent an individual from getting the flu, but it also helps reduce severe outcomes when someone does get sick with the flu. During past seasons, about 80 percent of flu-associated deaths in children have occurred in children who were not vaccinated.

Similarly, a recent study found that receiving the flu vaccine reduced severe outcomes in hospitalized patients by reducing deaths, reducing ICU admissions, reducing ICU length of stays, and reducing overall length of stay for hospital patients.

While the flu vaccine is currently the best tool to prevent illness, there is room for improvement. The CDC recently announced that this year's flu vaccine was only about 36 percent effective in preventing an individual from getting the flu. The vaccine's effectiveness varied from different age groups and for different strains of the virus. For example, the vaccine was 59 percent effective in children. However, it was much less effective in adults. For all age groups, the vaccine was only 25 percent effective this season against the deadliest strain of the flu, H3N2.

The vaccine's reduced effectiveness against H3N2, the most virulent and predominant strain of the flu this season, is especially concerning. Historically, we have struggled to make an effective vaccine against H3N2.

For example, during the 2014–2015 flu season, this committee closely examined the flu vaccine's reduced effectiveness due to the mismatch between the H3N2 strain used to develop the vaccine and the H3N2 strain that was actually circulating.

During the 2014–2015 season, the flu vaccine was only 9 percent effective because the H3N2 virus had mutated before the flu season began. This experience reminded us of the importance of being able to rapidly detect and respond to changes in the challenging and circulating flu viruses.

According to the FDA, this year, the vaccine's reduced effectiveness against the H3N2 virus was not caused by a mismatch. One factor that may explain why the flu vaccine was not that effective against the H3N2 strain is a mutation caused by the vaccine and egg adaptation through the egg-based manufacturing process.

Currently, about 80 to 85 percent of the flu vaccines are manufactured through the egg-based manufacturing process. When an inactivated flu virus is grown in chicken eggs during the vaccine

manufacturing process, genetic changes can occur in the virus that make the vaccine less effective in humans. Some researchers think that egg adaptation might be especially problematic for the H3N2 virus.

Of course, there are many different factors that also might explain the flu vaccine's reduced effectiveness for H3N2. This issue needs to be thoroughly investigated so we can improve the vaccine manufacturing process, if necessary, and improve the vaccine's effectiveness in the future.

I appreciate the hard work and dedication of the people at HHS to improve our flu preparedness, including those at CDC, NIH, ASPR, and FDA. One of our top priorities is to keep Americans healthy during flu season and improve the Federal public health response. And I look forward to today's testimony.

[The prepared statement of Mr. Harper follows:]

#### PREPARED STATEMENT OF HON. GREGG HARPER

Good morning. This year, like so many previous years, we've had a bad flu season. After months of record-breaking widespread flu activity, the CDC has reported that the flu season has finally peaked. We're probably still going to see flu activity until the middle of April, so if you have the flu or flu symptoms, it is important to see your doctor and stay home.

Influenza is a leading cause of death in the United States, especially in a severe flu season. Every year, thousands of Americans die from the flu and thousands more are hospitalized from flu-related complications. Since 2010, the flu has caused between 12,000 and 56,000 deaths per year. This year was no exception. Tragically, as of February 24, there had already been 114 influenza-associated pediatric deaths this season. Some of these deaths have occurred in my home State of Mississippi.

Although we've enhanced our preparedness for the flu in recent years, there is still room for improvement. The best way to prevent the flu is by getting your flu shot. Millions of Americans receive a flu shot every year to help protect them against illness. Unfortunately, there are a lot of Americans who do not get vaccinated. Last year, only 59 percent of children and about 43 percent of adults received the flu vaccination. Even though only a little over half of Americans typically get vaccinated, CDC estimates that flu vaccination prevented 3,000 pneumonia and influenza deaths during the 2015–2016 flu season alone. Increasing the number of Americans that get the annual flu vaccine will prevent more deaths and illnesses.

Not only can the flu vaccine help prevent an individual from getting the flu, but it also may help reduce severe outcomes when someone does become sick with the flu. During past seasons, about 80 percent of flu-associated deaths in children have occurred in children who were not vaccinated. Similarly, a recent study found that receiving the flu vaccine reduced severe outcomes in hospitalized patients by reducing deaths, reducing ICU admissions, reducing ICU length of stay, and reducing overall length of stay for hospital patients.

While the flu vaccine is currently the best tool to prevent illness, there is room for improvement. The CDC recently announced that this year's flu vaccine was only about 36 percent effective in preventing an individual from getting the flu. The vaccine's effectiveness varied for different age groups and for different strains of the virus.

For example, the vaccine was 59 percent effective in children; however, it was much less effective for adults. For all age groups, the vaccine was only 25 percent effective this season against the deadliest strain of the flu, H3N2.

The vaccine's reduced effectiveness against H3N2, the most virulent and predominant strain of the flu this season, is especially concerning. Historically, we have struggled to make an effective vaccine against H3N2. For example, during the 2014–2015 flu season, this committee closely examined the flu vaccine's reduced effectiveness due to the mismatch between the H3N2 strain used to develop the vaccine and the H3N2 strain that was circulating. During the 2014–2015 season, the flu vaccine was only 19 percent effective because the H3N2 virus had mutated before the flu season started. This experience reminded us of the importance of being able to rapidly detect and respond to changes in the circulating flu viruses.

According to the FDA, this year the vaccine's reduced effectiveness against the H3N2 virus was not caused by a mismatch. One factor that may explain why the

flu vaccine was not that effective against the H3N2 strain is a mutation caused by the vaccine and egg adaptation through the egg-based manufacturing process.

Currently, about 80 to 85 percent of the flu vaccines are manufactured through the egg-based manufacturing process. When an inactivated flu virus is grown in chicken eggs during the vaccine manufacturing process, genetic changes can occur in the virus that make the vaccine less effective in humans. Some researchers think that egg adaptation might be especially problematic for the H3N2 virus. Of course, there are many different factors that also might explain the flu vaccine's reduced effectiveness for H3N2. This issue needs to be thoroughly investigated so we can improve the vaccine manufacturing process if necessary and improve the vaccine's effectiveness in the future.

I appreciate the hard work and dedication of the people at HHS to improve our flu preparedness, including those at CDC, NIH, ASPR, and FDA. One of our top priorities is to keep Americans healthy during flu season and improve the Federal public health response. I look forward to today's testimony.

Mr. HARPER. The Chair will now recognize the ranking member, Ms. DeGette, for purposes of an opening statement.

**OPENING STATEMENT OF HON. DIANA DEGETTE, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF COLORADO**

Ms. DEGETTE. Thank you so much, Mr. Chairman.

I am always happy to have this flu hearing, which we seem to do every year. Looking at the witnesses, I feel like we are getting the band back together again to talk once again about what we can do.

I appreciate you all coming, and I am hoping that this year we can actually make some progress in talking about all of these issues that the chairman mentioned.

We have had in this subcommittee seven hearings on flu preparedness since 2004. Most recently, in 2015, we had two hearings after the country was hit with a particularly severe 2014 and '15 flu season, in which the H3N2 strain of flu predominated. This year, again, we are experiencing a severe flu season caused by the H3N2, and that is really a stark reminder of how the flu is very, very serious.

Hospitalizations have been high throughout the country. A hundred and fourteen children have died. As an example, my home State of Colorado set two records, not good records, this year, with nearly 4,000 people hospitalized due to flu and 160 flu outbreaks in long-term-care facilities.

As the chairman mentioned, this year's flu vaccine was only 36 percent effective, and that is of concern. Even I had the flu, and I had my vaccine, too.

And so, you know, this really is something that one would think in the year 2018 we would be able to tackle in a more meaningful way.

I understand that the FDA's Vaccine Advisory Committee just met to make recommendations for next year's vaccine. I am looking forward to hearing from the FDA about how data on this year's vaccine effectiveness helped to inform the decisionmaking for next year.

I am also hoping, as usual, to hear more about research efforts to produce a more broadly protective vaccine or even a universal vaccine that can target all strains of flu.



And, Mr. Chairman, we have talked in these various hearings over the years about the egg-based vaccines. And the mutation of the virus within the egg is only one of the problems with egg-based vaccines. When you look at the more remote but yet very real threat of a pandemic flu, if you are relying on egg-based vaccines, you can't be very nimble in producing vaccines in an effective and fast way.

And so I think that, this year, if it is any good news, a silver lining about the ravages of this flu season, maybe it will make the public understand how important this issue is for our public health agencies to address.

And I know all of our witnesses will remind us, even a vaccine with a low effectiveness rate will still protect millions from getting sick or may help mitigate the symptoms when people do get sick. And so, until we fix this system in a broader way, the flu vaccine is still our best tool.

But, unfortunately, the number of Americans who got a flu shot this year has not changed from our last hearing in 2015. I am hoping that that is another thing we can discuss, about how we can persuade people to get the vaccine and concrete steps that perhaps we can take next year.

As I said, we also have to work towards better treatment methods—in particular, more effective antiviral medications so that people who do become sick can be cared for before their illness becomes more serious. And I understand there are some of these medications in the pipeline right now. Maybe some of our witnesses can talk about these drugs that are in the pipeline, and also maybe they can talk about some of the spot shortages we saw this past season.

Finally, the importance of a strong public health infrastructure cannot be overstated. Because of the critical work of Federal and State public health experts, we are always in a good position, but there is still more that needs to be done. And I am looking forward to hearing how we can coordinate our strategies across all levels of Government.

So, Mr. Chairman, again, I want to thank the witnesses who are here today, some of which I have worked with for years. They are true public servants and truly dedicated to tackling this issue. And I know they will be our partners in this committee as we continue to go forward.

Thanks, and I yield back.

[The prepared statement of Ms. DeGette follows:]

#### PREPARED STATEMENT OF HON. DIANA DEGETTE

Thank you, Mr. Chairman, for convening this important hearing. This is a bipartisan issue, and I look forward to finding areas where we can work together on preparing our Nation against this threat.

Flu preparedness and response is incredibly important, and the committee has a long history of addressing this issue. We have held seven hearings on flu preparedness since 2004. Most recently, in 2015, we held two hearings after the country was hit with a particularly severe 2014–15 flu season in which the H3N2-strain of flu predominated.

This year, we are again experiencing a severe flu season caused by H3N2. It has been a stark reminder of just how serious the flu can be.

Hospitalizations have been high throughout the country, and 114 children have died.

As an example, my home State, Colorado, has set two records this year, with nearly 4,000 people hospitalized due to flu, and 160 flu outbreaks in long term care facilities.

I am troubled by the news that this year's flu vaccine was only 36 percent effective, although I realize that this number is different for different age groups.

I want to hear from our witnesses today about what "36 percent effective" means, and what research must be done to help our seasonal flu vaccine offer more protection.

I understand that FDA's vaccine advisory committee actually just met to make recommendations for next year's vaccine. I hope that FDA will tell us how data on this year's vaccine effectiveness helped to inform decision for next year.

I also hope that we will hear more about research efforts designed to produce a more broadly protective vaccine, or perhaps even a universal vaccine that can target all strains of flu.

I know that the flu virus is particularly hard to vaccinate against, but I also know that we have some of the brightest minds in the country working on this issue.

I am sure that I echo the thoughts of many of my colleagues when I say that work towards better vaccine must be a priority for our public health agencies.

As our witnesses will remind us today, though, even a vaccine with a low effectiveness rate will still protect millions from getting sick. The flu vaccine remains the best tool we have to protect as many people as possible.

Only around forty percent of Americans received a flu shot this year. This number has not changed from the last time we had a flu hearing, in 2015. We can and must do better, and I hope that our witnesses today are prepared to discuss concrete steps that we can take to increase vaccination rates in this country.

We also must work towards better treatment methods, in particular more effective antiviral medications, so that people who do become sick can be cared for before their illness becomes more serious.

I hope that our witnesses today will describe the new drugs in the pipeline. I also hope that they are prepared to address the spot shortages we saw this past season, which may have prevented some individuals from being treated as quickly as they otherwise might have been.

Finally, the importance of a strong public health infrastructure that allows us to prepare and respond cannot be overstated.

Because of the critical work of our Federal and State public health experts, we are in a good position, but there is always more work to be done. We need coordinated response capabilities, effective communication strategies, and critical investments so we can strengthen our response to seasonal flu.

I look forward to hearing about how far we have come and what more needs to be done to strengthen our national preparedness.

Mr. Chairman, let me conclude by acknowledging and thanking the witnesses and the agencies before us today. We are fortunate to have your talent on the frontlines in the ongoing fight against infectious diseases, including influenza.

We should thank you by ensuring that you always have the tools and resources you need to remain on the cutting edge of science and preparedness, and I hope you can tell us what you need going forward.

I look forward to working together to move the country toward better flu preparedness.

Ms. DEGETTE. Oh, also, I would ask unanimous consent to put Mr. Pallone's opening statement in the record. He will not be able to come today.

Mr. HARPER. Without objection.

[The prepared statement of Mr. Pallone appears at the conclusion of the hearing.]

Mr. HARPER. The gentlewoman yields back.

The Chair now recognizes the chairman of the full committee, Mr. Walden, for the purposes of an opening statement.

#### **OPENING STATEMENT OF HON. GREG WALDEN, A REPRESENTATIVE IN CONGRESS FROM THE STATE OF OREGON**

Mr. WALDEN. I thank the chairman, and I thank our witnesses for being here today.

You know, this has been, I think, one of the most severe flu seasons in the United States that we have seen. Nearly 50,000 people die in a single season. Today, we are currently experiencing a severe flu season with a predominantly deadly strain, by all accounts. It is vital to find ways to reduce deaths and hospitalizations from this challenging and changing virus.

At Energy and Commerce, and this subcommittee in particular, we have a long history, as you have heard, of connecting these oversight hearings and trying to be as helpful as we can to you all as we work on the public policy.

During our last hearing, in November of 2015, we explored many important issues, including how the Department of Health and Human Services could help improve our ability to respond to seasonal flu vaccine mismatches.

For more than 70 years, most flu vaccines have been made through an egg-based process, and over the last decade we have seen some innovation in the manufacture of the annual flu vaccine. The FDA approved the first flu vaccine manufactured using cell culture technology in 2012. And the FDA approved the first flu vaccine manufactured using recombinant DNA technology in 2013.

And in addition to new manufacturing technologies and methodologies, we have also seen new types of flu vaccine made available for the American people. Historically, flu vaccines, I understand, have been offered to protect against three different strains of flu virus. And, in 2012, the FDA approved the first flu vaccine that offered protection against four different strains. In '09, the FDA approved the first high-dose flu vaccine for older adults, and some data show that the high-dose flu vaccine is more effective in older individuals than the normal dose.

Now that we have different ways to manufacture the flu vaccine, we need to ensure we have enough data and information to make sure we are making the most effective seasonal flu vaccine possible. The FDA recently announced that preliminary data show that the cell-based flu vaccine might be somewhat more effective, I understand, in preventing the flu than the egg-based vaccine this season. We need to understand why that might be and why there are differences in effectiveness so we can improve vaccine manufacturing processes as necessary.

As Subcommittee Chairman Harper has said and emphasized, the annual flu vaccine is still the best defense. Every year, thousands of lives are saved because people get that vaccine.

And so, if you do get the flu, there are antivirals, as we all know. And we have heard—I can't remember a flu season where more people I know have said, "Oh, yeah, I got Tamiflu" or "Somebody I know got Tamiflu" or whatever the antivirals are. So that is an important part of this, as well. And I would love for you to talk a bit about what has been in the press about the Japanese product, apparently, in Japan that might cut off the flu even sooner and what you see on that one, if anything.

And one day we hope to have a universal vaccine. We are encouraged by the National Institute of Allergy and Infectious Disease's recent release of a strategic plan for developing a universal flu vaccine.

I am also glad we have all of you here today and the director of the Biomedical Advanced Research and Development Authority here to share the information that you all are working on. So thank you.

[The prepared statement of Mr. Walden follows:]

#### PREPARED STATEMENT OF HON. GREG WALDEN

Thank you, Mr. Chairman, for holding this hearing on the very important issue of public health preparedness for and response efforts to the seasonal influenza. America is experiencing a severe flu season with a predominant deadly strain. In a bad flu season, more than 50,000 people die, nearly as many as the Nation lost during the Vietnam War. It is vital to find ways to reduce deaths and hospitalizations from this challenging virus.

This is the reason why the committee has a long history of conducting oversight of the effectiveness of the flu vaccine and the Federal Government's overall response to the seasonal influenza. During our last hearing in November 2015, we explored many important issues including how HHS could help improve our ability to respond to seasonal flu vaccine mismatch.

For more than 70 years, most flu vaccines have been made through an egg-based process. Over the last decade, we have seen some innovation in the manufacturing of the annual flu vaccine. FDA approved the first flu vaccine manufactured using cell culture technology in 2012, and FDA approved the first flu vaccine manufactured using recombinant DNA technology in 2013.

In addition to new manufacturing methodologies, we've also seen new types of flu vaccines available for Americans. Historically, flu vaccines have offered protection against three different strains of the flu virus. In 2012, however, FDA approved the first quadrivalent flu vaccine that offered protection against four different strains of the flu virus. In 2009, FDA approved the first high-dose flu vaccine for older adults and some data shows that the high-dose flu vaccine is more effective in older individuals than the normal dose.

Now that we have different ways to manufacture the flu vaccine, we need to ensure that we have enough data and information to make sure we're making the most effective seasonal flu vaccine possible. FDA recently announced that preliminary data shows that the cell-based flu vaccine might be somewhat more effective in preventing the flu than the egg-based vaccine this season. We need to understand why there might be a difference in effectiveness, so we can improve the vaccine manufacturing process if necessary.

As Subcommittee Chairman Harper appropriately emphasized in his opening statement, the annual flu vaccine is the best way to prevent the flu. Every year, thousands of lives are saved by the flu vaccine. According to the CDC, flu vaccination during the 2015–2016 flu season prevented about 5.1 million illnesses, 2.5 million medical visits, 71,000 hospitalizations, and 3,000 pneumonia and influenza deaths. That's a lot of people that were helped by the flu vaccine. Even with below-average overall effectiveness, this year's vaccine was about 60 percent effective for children aged 6 months to 8 years.

If you do get the flu, there are antivirals available to treat your illness. We look forward to hearing from CDC today about their education and outreach strategies to ensure providers and patients are aware of the importance of antivirals to treat the flu.

One day, we hope to have a universal vaccine and we're encouraged by the National Institute of Allergy and Infectious Diseases' recent release of a strategic plan for developing a universal flu vaccine. I know that we're still a long way from having a universal vaccine, but I'm looking forward to hearing updates from NIH today on our progress in achieving this goal and the challenges that we face in developing a universal vaccine. I'm also glad that we have BARDA here today to share information about their work in helping to develop better flu vaccines and improve seasonal and pandemic influenza preparedness.

I would be remiss if I didn't mention the related issues of pandemic influenza preparedness. Last year, the committee wrote to HHS about the status of the Pandemic Influenza Plan, which had not been updated in quite some time. I was pleased that HHS released the updated plan not long after receiving our letter, and recognized that pandemic and seasonal influenza planning are interdependent because of the continually changing nature of flu viruses.

I appreciate the hard work and dedication of the people at HHS to protect Americans from the flu and its deadly consequences. I'm looking forward to our conversa-

tion today and to learning more about how we can continue to improve our preparedness for, and response to, the seasonal influenza.

Mr. WALDEN. And, with that, I would yield the remainder of my time to the chairman of the Health Subcommittee, the good doctor from Texas, Dr. Burgess.

Mr. BURGESS. Thank you, Mr. Chairman.

And I want to thank our witnesses for taking the time to testify before us today. Most of you are well-known to this subcommittee.

The flu has hit many of our districts with astonishing force this year. The district that I represent in north Texas, our public health departments were strained. We had schools that had to close temporarily to prevent the spread of flu amongst children. Since the start of this flu season, more than 400 people in my area have been hospitalized as a result of the flu. Twelve reported influenza-associated deaths, including one pediatric death.

Earlier this year, the Health Subcommittee was briefed by Dr. Fauci and someone from the CDC about the development and effectiveness of this year's flu vaccine. The timing of this particular hearing is appropriate, given that we are just past the peak of flu season, and now people are working on the development of next year's vaccine, and we are all anxious to hear what awaits for next year.

Mr. Chairman, thank you for holding this important and timely hearing, and I certainly look forward to hearing from our witnesses. And I yield back.

Mr. HARPER. The gentleman yields back.

I ask unanimous consent that the Members' written opening statements will be made part of the record.

Without objection, they will be entered into the record.

Additionally, I ask unanimous consent that Energy and Commerce members not on the Subcommittee on Oversight and Investigations be permitted to participate in today's hearing.

Without objection, so ordered.

I now would like to introduce our witnesses for today's hearing.

First, today, we have doctor Anne Schuchat, the Acting Director for the Centers for Disease Control and Prevention.

We welcome you today.

Second, we have Dr. Anthony Fauci, the Director of the National Institute of Allergy and Infectious Diseases at the National Institutes of Health.

Then we have Dr. Rick Bright, the Deputy Assistant Secretary for Preparedness and Response and Director of the Biomedical Advanced Research and Development Authority at the Office of the Assistant Secretary for Preparedness and Response, which means there's no way that gets on a business card.

But we're glad to have you here.

And, finally, the Honorable Scott Gottlieb, who serves as the Commissioner for the U.S. Food and Drug Administration.

I want to thank you each for being here. This is a very important topic, and we look forward to having this discussion today.

Are you each aware that the committee is holding an investigative hearing and, when so doing, we have the practice of taking testimony under oath? Does anyone have an objection to testifying under oath?

Seeing none, the Chair then advises you that, under the rules of the House and the rules of the committee, you are entitled to be accompanied by counsel. Do any of you desire to be accompanied by counsel for the purposes of today's hearing?

Seeing none, in that case, if you would please rise and raise your right hand, and I will swear you in.

[Witnesses sworn.]

Mr. HARPER. You are now under oath and subject to the penalties set forth in title 18, section 1001 of the United States Code. And you may now each give a 5-minute summary of your written statement.

And we will begin first with Dr. Schuchat, and you are now recognized for 5 minutes.

**STATEMENTS OF ANNE SCHUCHAT, M.D., ACTING DIRECTOR, CENTERS FOR DISEASE CONTROL AND PREVENTION, DEPARTMENT OF HEALTH AND HUMAN SERVICES; ANTHONY S. FAUCI, M.D., DIRECTOR, NATIONAL INSTITUTE OF ALLERGY AND INFECTIOUS DISEASES, NATIONAL INSTITUTES OF HEALTH, DEPARTMENT OF HEALTH AND HUMAN SERVICES; RICK BRIGHT, PH.D., DEPUTY ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE, AND DIRECTOR, BIOMEDICAL ADVANCED RESEARCH AND DEVELOPMENT AUTHORITY, OFFICE OF THE ASSISTANT SECRETARY FOR PREPAREDNESS AND RESPONSE, DEPARTMENT OF HEALTH AND HUMAN SERVICES; AND SCOTT GOTTLIEB, M.D., COMMISSIONER OF FOOD AND DRUGS, FOOD AND DRUG ADMINISTRATION, DEPARTMENT OF HEALTH AND HUMAN SERVICES**

#### **STATEMENT OF ANNE SCHUCHAT**

Dr. SCHUCHAT. Good morning, Mr. Chairman and members of the committee.

Influenza is a formidable adversary. The virus is ever-changing, it is with us every year, and it's too often able to outsmart our immune systems. At CDC, we have worked with domestic and global partners to build cutting-edge systems to characterize influenza viruses and the disease they cause and to monitor vaccine effectiveness.

We know that people are concerned about this flu season, and that concern is warranted. Influenza can be a very serious threat to the health of Americans. And despite the progress we've made, we have much more work to do.

I'll provide brief updates about this season and the work that CDC is doing to improve the tools for influenza prevention and control.

As you've heard, this has been a severe season. Hospitalizations have broken records. Influenza-like illness presenting to doctors' offices and emergency departments at its peak was about as high as we saw during the pandemic of 2009. Too many children have died already from influenza this season. We had intense activity in virtually the whole country at the same time, and that contributed to some of the spot shortages of antivirals. We are not over with the season. Disease is decreasing, but the B strains are starting to be as common as the H3N2 strains.

As you've heard, the vaccine effectiveness this season was lower than usual. It was at 36 percent overall and even lower for the H3N2 strains that dominated. Children did receive better protection from the flu vaccine—59 percent effectiveness in children and about 50 percent effectiveness against the H3N2 strain—a reminder that vaccinating children can be lifesaving against flu. Sadly, the vast majority of children who die from influenza have not received any vaccine at all.

There are many theories about why influenza vaccines work less well against the H3N2 strains. One theory is that there are egg-adapted changes that occur in the process of developing the vaccine. There may be differences in effectiveness based on prior immunization or prior exposure to flu strains.

We are still characterizing the viruses for this year. We do not think there was antigenic drift, but there may be some changes in the viruses that could account for the severe season. That's still under study.

Some vaccine is better than no vaccine protection. We wish the vaccines worked better, but we do know that the vaccines are providing protection to many and they're mitigating the severity of the disease.

CDC has three objectives in our work with vaccines. We want to maximize use of the current vaccines. We want to support the NIH's leadership in developing a universal vaccine. And, in the near term, we want to improve the current vaccines that we have.

We have made significant progress since the 2009 pandemic. We have more data than ever before. We have more information on vaccine effectiveness from our multi-State network. We are producing more potential vaccine candidates. We are collecting more information on the genomic characteristics of the viruses using next-generation sequencing. We are working with pharmacies, long-term-care facilities, and insurers to address the spot shortages of antivirals and were able to smooth things out a bit during this season, but we know people were still frustrated.

But, despite the progress we've made, there is much more to learn about influenza. And we think that investing in that learning can have direct implications for prevention and control.

In closing, I know this has been a difficult flu season and a heartbreaking one for too many families. Flu continues to be a priority for the CDC. We are literally working 24/7 on this issue. And we are all, across HHS, committed to working together to find ways and tools to help Americans reduce their risk of getting sick.

I look forward to answering your questions.

[The prepared statement of Dr. Schuchat follows:]



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**Testimony before the  
Committee on Energy and Commerce  
Subcommittee on Oversight and  
Investigations  
United States House of Representatives**

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**U.S. Public Health Preparedness for and Response Efforts to  
Seasonal Influenza**

**Anne Schuchat, MD (RADM, USPHS)**

**Acting Director, Centers for Disease Control and Prevention,  
U.S. Department of Health and Human Services**



**For Release upon Delivery**

**March 8, 2018**

**Expected at 10:00 a.m.**



Good morning Chairman Harper, Ranking Member DeGette, and Members of the Committee. I am Dr. Anne Schuchat, Acting Director of the Centers for Disease Control and Prevention (CDC) and Acting ATSDR Administrator. I want to thank the Committee for the opportunity to provide an update on the current influenza (flu) season and for bringing attention to this ongoing and very serious public health threat. CDC works collaboratively with our colleagues in other components of the Department of Health and Human Services to protect the nation's health. I and the CDC leadership team are committed to ensuring that CDC will continue to conduct critical science, provide health information and act quickly to protect our nation through the control and prevention of disease, injury, and disability in the United States and globally.

At CDC we have spent decades building the surveillance and diagnostic capacity to rapidly detect, prevent and respond to annual influenza epidemics, and emerging novel and pandemic influenza threats. Seasonal and pandemic influenza prevention and response are inextricably linked, as preparedness for seasonal flu ensures preparedness for an influenza pandemic. CDC leads efforts that span from detection of influenza to protection against the ever-changing virus. Our systems provide the scientific basis for vaccine virus selection – for each year's seasonal flu vaccine as well as for pandemic vaccine stockpiling. We diligently monitor for genetic changes in the flu virus, and identify how those genetic changes affect disease transmission and severity. We build public awareness and provider knowledge about prevention methods and early treatment with antivirals, and support public sector delivery of routine and emergency immunizations. Throughout each season, we monitor both the safety and effectiveness of influenza vaccine, and today I will provide some more information specifically about our systems to monitor vaccine effectiveness and highlight some of the work we are doing to improve vaccines. We are better prepared than we have ever been to detect, prevent, treat, and respond to influenza; however, despite the progress we have made in fighting the flu, seasonal influenza viruses constantly change and are adept at outfoxing our immune systems. It is critical that we deepen our

understanding of influenza and use this knowledge to make near-term improvements to influenza vaccines.

This year's influenza season has been challenging across the United States, and has been heartbreaking for families who have lost loved ones. Every year influenza causes significant burden in this country with many millions of Americans becoming ill, hundreds of thousands of them requiring hospitalization, and tens of thousands dying.

The 2017-2018 influenza season has been a severe one. Flu activity began to increase in early November and then increased rapidly from December through early February. This season, the levels of influenza-like illness, which is a measure based on outpatient visits and emergency department visits, reached levels as high as at the peak of the 2009 H1N1 flu pandemic. Unlike in other seasons when flu activity varied in timing and intensity across states, during this 2017-2018 season, many states experienced widespread and high flu activity at the same time. We cannot predict how long this season will last, and while we have started to see a decline in rates of people visiting their doctor for influenza-like illness, we expect to see several more weeks of ongoing flu activity, with continued reports of hospitalizations and flu deaths in children and adults.

The majority of people with influenza so far this season have been infected with the H3N2 influenza virus. During H3N2 predominant seasons, we see more cases, more visits to the doctor, more hospitalizations, and more deaths, especially among older people. It is still too early to assess the full burden of influenza disease for this year, but estimates from recent seasons where H3N2 was predominant, like the 2012–13 and 2014–15 seasons, provide an indication of what to anticipate for this season. CDC estimated that during seasons like those, influenza accounted for as many as 35.6 million illnesses, 16.6 million medically attended visits, 710,000 hospitalizations, and 56,000 deaths.

CDC recommends a yearly flu vaccine for everyone six months of age and older as the most important step in preventing influenza infection. Flu vaccines protect against three or four different flu viruses. Three-component vaccines contain an H3N2, an H1N1, and a B virus. Four-component vaccines have an additional B virus component. Unfortunately, flu vaccines do not usually work as well against H3N2 viruses; however, even with reduced vaccine effectiveness, vaccination can prevent flu deaths, illnesses, medical visits, and hospitalizations. Among flu-associated pediatric deaths in the United States from 2010 to 2016, 78 percent of children who died had not been fully vaccinated.

The influenza vaccine production process requires that virus strains be selected in February of each year for vaccine that will be used to protect Americans in the fall. Throughout the year, CDC studies thousands of flu viruses in our laboratory to evaluate whether the currently circulating flu viruses have changed, or drifted, over the months since selection of the virus strains. So far this season, we are not seeing significant drift in the currently circulating viruses, including the H3N2 viruses that are predominating.

Where we are seeing differences is when we compare the vaccine viruses prepared for manufacturing egg-based influenza vaccine to those that are currently circulating. These differences are notable for the H3N2 viruses; unfortunately, the adaptation to growth in eggs makes the H3N2 vaccine viruses less similar to the circulating wild-type H3N2 viruses in the community. These egg-adapted changes are likely one of several possible contributors to the relatively lower vaccine effectiveness typically seen against H3N2 viruses compared with H1N1 or influenza B viruses.

CDC has developed and maintains the nation's system for monitoring the effectiveness of influenza vaccines. This network's routine data inform recommendations on vaccine use, selection of new viruses for updating the vaccines, communication to the public, and sharing important information for manufacturers regarding the performance of their vaccines. In February, CDC published its interim estimates for this season's vaccine effectiveness (VE). CDC found that vaccination this season has

reduced the risk of having to go to the doctor for flu by 36 percent so far, and that flu vaccine is offering substantial protection against H1N1 flu (67 percent) as well as moderate protection against flu B viruses (42%). Vaccine effectiveness against this season's dominant H3N2 viruses is about 25 percent, similar to what CDC expected at the beginning of the season. These results are also similar to the final U.S. vaccine effectiveness estimates of 32 percent against H3N2 viruses reported last season (2016-2017). Importantly, the vaccine offered better protection against H3N2 for children six months to eight years old, with estimated effectiveness of 51 percent. Overall, the vaccine is 59 percent effective against both influenza A and B in children six months to eight years of age.

Over the last three years, CDC has significantly improved our global surveillance and characterization of influenza viruses in support of more effective vaccines. Globally coordinated epidemiologic and virologic surveillance is the foundation of the influenza vaccine virus selection and development process. The World Health Organization (WHO) Global Influenza Virus Surveillance and Response System (GISRS) is a global network that provides year-round surveillance of influenza viruses. Within GISRS, CDC serves as one of five Collaborating Centers that receive and characterize thousands of influenza viruses each year. CDC has expanded domestic and global disease surveillance and laboratory detection capacity to support improvements in vaccine virus selection and in flu vaccine effectiveness. CDC contributes a large amount of data for both the U.S. and global viruses, and is an innovator in new methods for the strain selection process. Key activities include partnerships with more than 50 Ministries of Health and other health agencies to strengthen global influenza surveillance, develop new technologies, such as next-generation sequencing, to analyze and characterize flu viruses more quickly, and to increase the number of egg-derived viruses CDC produces to expand options for suitable vaccine development.

Still, more can and needs to be done to support development of better vaccines. CDC continues to support the long-term goal of developing longer-lasting, more broadly protective “universal” influenza vaccines in collaboration with HHS agency partners, and to focus on incremental vaccine improvements that would provide better tools to prevent influenza. Until better vaccines are available, CDC focuses on optimizing use of the currently available vaccines.

Thank you for the opportunity to talk about CDC’s role in the 2017-2018 influenza season. I am happy to answer any questions you may have.

Mr. HARPER. Thank you very much.

The Chair will now recognize Dr. Fauci for 5 minutes for the purposes of his opening statement.

#### STATEMENT OF ANTHONY S. FAUCI

Dr. FAUCI. Thank you very much, Mr. Chairman, Ranking Member DeGette, Chairman Walden, members of the committee. Thank you for giving me the opportunity to talk to you about the role of the National Institute of Allergy and Infectious Diseases at the NIH in addressing seasonal and pandemic influenza.

All right. Next slide.

As you can see, as I have testified before this committee multiple times, that the NIH research in this case in influenza is multifaceted, involving basic research, research resources, clinical research, ultimately with the development of countermeasures in the form of diagnostics, therapeutics, and vaccines. For the purpose of today's discussion, I'll focus only on vaccines.

If I can have the next slide.

As seen in this slide, as mentioned before—and let me start off by reiterating what you said, what Ms. DeGette said, and what Anne Schuchat said, is that it is always better to get vaccinated than not to get vaccinated.

But, in that reality, we can do better with the vaccines that we have, because the current influenza vaccines are not consistently effective. We have an example of that this year. Also, pandemics occur, and the responses are generally not very effective. We've seen that with the 2009 pandemic flu, and we continue to chase after potential pandemics like H5N1, H7N9.

Next slide.

The major challenges in influenza vaccinology is we need to improve on the current influenza vaccines. We need to improve the production of these from egg-based to cell-based to recombinant DNA technology, and I'll get back to that in a moment. And, also, we need to, as Anne mentioned, develop universal influenza vaccines for broad coverage.

Next slide.

Egg-based technology is time-honored indeed, it has been effective, but it's antiquated. We need to graduate into the 21st century. Cell-based is better, but recombinant DNA technologies that I'll get into in a moment, which will be the tools to which we develop a universal flu vaccine, is the way of the future.

Next slide.

When you talk about improving seasonal influenza preparedness, that essentially marries you to preparing for a pandemic. And I'll explain what I mean.

Next slide.

I wrote an article just recently when we got into the problem of the growing in eggs, with the adaptation in eggs leading to a less effective vaccine, to emphasize the need for a universal flu vaccine.

Next slide.

Now, let me talk to you a little bit about that, because there are some mechanisms that are simple now but nonetheless were not fully appreciated before we really understood the structural biology of these viruses.

On the left-hand part of this slide is an influenza model. That's the virus. The arrow points to one protein, the hemagglutinin molecule, which is the part that binds to the cell receptor that gets you and I sick when we get the flu.

Next slide.

Now, a very interesting thing was noticed several years ago, is that this is made up, this molecule, of a head and a stem. Now, this is the way it really looks like, but if you want to emphasize it, think of a broccoli with a head and a stalk or a mushroom with a cap and the stalk. The head is the part that the immune system makes a response against. That's the good news.

The bad news is that that head is one that has many mutations that change from season to season—the drift that Dr. Schuchat spoke about and that Ms. DeGette spoke about. The stem, however, has few mutations. The little red dots are the mutations. So the trick is, how do you make a response selectively against the part of the virus that does not change as opposed to one that does change?

Next slide.

There are a number of ways of doing that. I'm going to just show you one example among many.

Investigators at the NIH and funded by the NIH have a situation now where they can take that molecule, that hemagglutinin, and essentially shave off the head. It's called a headless stem. Now, normally, that would fall apart, but it doesn't fall apart, because investigators at the Vaccine Research Center have made mutations in the molecule to keep it stable.

And what we've done, we've put on what's called a nanoparticle. That's on the far right of the slide. This is what it looks like 10 million times blown up. So this is a little particle, but all of these are stems, so that when the immune system sees that, it doesn't get distracted about anything else and it focuses in on making an antibody or a cell-mediated response against something that does not change.

Next slide.

Now, we recently, in June of this year, had a workshop in Rockville, Maryland, where we called together experts from the United States and throughout the world to help us at NIH to develop what we call a pathway to a universal influenza vaccine.

Next slide.

And I'm happy to say that just a few days ago we recently published our strategic plan and our research agenda in *The Journal of Infectious Diseases* to help us get to the goal that I've just been describing over the last 5 minutes.

Thank you.

[The prepared statement of Dr. Fauci and his slide presentation follow:]

DEPARTMENT OF HEALTH AND HUMAN SERVICES

NATIONAL INSTITUTES OF HEALTH

National Institute of Allergy and Infectious Diseases Research Addressing  
the Public Health Threat of Influenza

Testimony before the

House Committee on Energy and Commerce

Subcommittee on Oversight and Investigations

Anthony S. Fauci, M.D.

Director of the National Institute of Allergy and Infectious Diseases

March 8, 2018



Mr. Chairman, Ranking Member DeGette, and members of the Subcommittee, thank you for the opportunity to discuss the response of the National Institutes of Health (NIH) to the public health threat posed by influenza. I direct the National Institute of Allergy and Infectious Diseases (NIAID), the lead NIH institute for conducting and supporting research on established and emerging infectious diseases, including influenza.

NIAID funds a longstanding, comprehensive portfolio of basic, translational, and clinical research on influenza focused on better understanding the virus and the disease that it causes as well as developing diagnostics, therapeutics, and vaccines to prevent and treat it. The current, remarkably severe influenza season, the consistently changing nature of seasonal influenza viruses, together with the ever-present threat of pandemic influenza, underscore the importance of this research to improve on our current influenza vaccines, as well as to lead us on a pathway toward the development of a universal influenza vaccine. The latter would provide long-lasting protection against multiple seasonal and pandemic influenza viruses. NIAID efforts in this regard are bolstered by ongoing collaborations with academia, philanthropic organizations, biotechnology and pharmaceutical companies, as well as U.S. government partners, particularly the Centers for Disease Control and Prevention (CDC), the Food and Drug Administration (FDA), and the Office of the Assistant Secretary for Preparedness and Response (ASPR), including the Biomedical Advanced Research and Development Authority (BARDA).

**Fundamental Research to Understand Influenza Evolution and Immunity**

NIAID-supported basic research on influenza provides the foundation for developing new and improved diagnostics, antiviral therapies, and vaccines for influenza caused by both seasonal and pandemic virus strains. Detailed studies of how our immune system responds to influenza viruses and influenza vaccines are stimulating novel approaches for developing vaccine candidates that can elicit robust immune responses and provide broad protection against a variety of influenza virus strains. In accordance with the highest bioethical and scientific standards, NIH clinical researchers are investigating human influenza infection under carefully controlled conditions in which healthy volunteers are challenged with influenza virus. The scientists are closely examining the course of influenza infection from the moment of exposure to the virus to determine when viral shedding occurs, when symptoms begin and end, and when the body begins to mount an immune response against the virus. The researchers also are studying factors correlated with protection against influenza. These influenza challenge studies will serve as an efficient way to evaluate the safety and efficacy of novel approaches to treat or prevent influenza infection. The findings from these studies already are informing the design of future clinical trials to evaluate candidate influenza countermeasures, including vaccines. Additionally, NIAID is soliciting research proposals for studies that will follow cohorts of infants to determine how natural influenza infections and/or influenza vaccinations shape their responses to future influenza virus exposures as they enter adolescence and adulthood. The ultimate goal of this research is to provide key information to facilitate the design of broadly and durably protective influenza vaccines.

NIAID also supports research to better understand the transmission, evolution, and pathogenesis of influenza viruses in animals and humans to inform the development of broadly protective influenza vaccines. For example, the NIAID Centers of Excellence for Influenza Research and

Surveillance (CEIRS) study the emergence and spread of novel influenza viruses worldwide to lay the groundwork for new and improved control measures for circulating influenza viruses. The CEIRS global network of research sites has characterized newly detected influenza virus strains and has evaluated potential vaccine approaches for emerging influenza viruses, including those of avian origin. CEIRS investigators also have recapitulated influenza virus evolution in the laboratory, allowing them to predict viral mutations that may occur in nature. This information can be used to help design seasonal influenza vaccines that optimally match circulating strains. Influenza virus surveillance programs using next-generation genomic technologies supported by NIH also are providing an in-depth view of influenza virus evolution and insights into reducing the disease burden of seasonal and pandemic influenza.

### **Influenza Vaccines**

#### *Challenges Presented by Current Influenza Vaccines*

Licensed annual influenza vaccines, the primary tool for prevention of seasonal influenza, are updated each year to address the strains that experts deem likely to circulate during the upcoming influenza season. These vaccines are updated annually through supplements to their FDA licenses, which must be approved by FDA prior to distribution of the vaccines. The overall efficacy of seasonal influenza vaccines ranges from 40 to 60 percent when there is a good match between the vaccine and circulating influenza viruses, although they may be significantly less effective when varying degrees of mismatches occur between the circulating strains and the vaccine. These mismatches can be caused by the constant evolution of circulating influenza strains, as was observed in the 2014-2015 influenza season, or by mutations that occur when

viruses from humans are adapted to grow in eggs, a requirement for the egg-based vaccine manufacturing process, the predominant technology used for influenza vaccines globally.

The public health response to influenza becomes particularly challenging when a pandemic strain emerges. This happens when the vast majority of the population has not been exposed to a newly emerging influenza strain and lacks immunity to it, as occurred with the 2009 pandemic H1N1 influenza virus. The less than optimal efficacy of vaccines against seasonal influenza together with the constant threat that a pandemic strain may emerge, and the risk of seasonal influenza vaccine mismatches, emphasize the need for additional strategies to address both seasonal and pandemic influenza. A more broadly protective, or universal, influenza vaccine would be a valuable tool in our efforts to generate more durable protection against multiple influenza strains. It would also be important as we are pursuing the development of a universal influenza vaccine to improve on the efficacy of our current vaccines since it will take several years to develop a universal influenza vaccine ready for widespread use.

#### *Universal Influenza Vaccines*

NIAID has made the development of universal influenza vaccines a high priority, and in this regard, has begun a concerted effort to galvanize research in the field. On June 28-29, 2017, NIAID convened a group of domestic and international influenza experts at a research agenda-setting workshop, “Pathway to a Universal Influenza Vaccine.” Following this meeting, NIAID outlined its research priorities in a Strategic Plan for a Universal Influenza Vaccine published online on February 28, 2018, by the *Journal of Infectious Diseases*. The Strategic Plan focuses on three research areas: improving knowledge of the transmission, natural history, and pathogenesis of influenza infection; characterizing influenza immunity and immune factors that

correlate with protection against influenza; and supporting the rational design of universal influenza vaccines. Targeted investments in each of these research areas will be required to generate the critical information necessary to enable the development of universal vaccines effective against both seasonal and pandemic influenza.

*Strategies for Universal Influenza Vaccines*

Current NIAID research on universal influenza vaccines pursues multiple strategies that target parts of the influenza virus common across multiple influenza strains in an effort to broaden the immune system response and cover multiple, diverse influenza viruses. One scientific challenge in developing a truly universal vaccine relates to the influenza surface protein hemagglutinin (HA). Most antibodies against influenza virus target the “head” of the mushroom-shaped HA protein, which differs from strain to strain of influenza viruses and is constantly changing by mutation. In contrast, the “stem” of the mushroom-shaped HA protein remains relatively constant among diverse influenza virus strains, suggesting that strategies to generate immune responses against the HA stem could elicit broader protection against multiple influenza virus strains.

Scientists at the NIAID Vaccine Research Center (VRC) have developed a vaccine candidate consisting of a ferritin nanoparticle to which is attached multiple copies of the stabilized headless stem of the HA protein from an H1N1 influenza virus. This vaccine more effectively elicits an immune response specifically against the stem and protected animals against lethal influenza infection. Notably, the vaccine protected against a different influenza subtype (H5) than the H1 subtype upon which it was based, providing a proof-of-concept that vaccines targeting the HA stem could offer broad protection against diverse influenza strains.

In addition, VRC researchers have conducted several clinical trials of another influenza vaccine strategy designed to elicit enhanced and broadly reactive antibody responses. Recent NIAID Phase I clinical trials have tested an initial vaccination with an influenza virus DNA vaccine candidate known as a “prime” followed by a “boost” with a standard inactivated seasonal influenza vaccine. The clinical trials demonstrated that such regimens were safe and produced anti-influenza A immune responses. NIAID intramural scientists also are evaluating a universal influenza vaccine consisting of a cocktail of avian influenza viruses comprised of either virus-like particles or inactivated vaccine strains. Both vaccine regimens protected mice and ferrets from infection with a wide range of influenza A strains, including strains not contained in the vaccine, suggesting another potential strategy to develop a universal influenza vaccine. NIAID plans to conduct Phase I safety and immunogenicity studies of this vaccine approach by next year. NIAID continues to evaluate each of these vaccine strategies to better understand how they could contribute to the design of universal influenza vaccines.

NIAID also is pursuing novel vaccine approaches that may induce or boost broadly protective immune responses by targeting other conserved influenza proteins such as the nucleoprotein (NP) and the ion channel matrix protein (M2). In addition, NIAID is planning a Phase II clinical trial of M-001, a vaccine candidate that contains several influenza fragments recognized by the immune system that are common among multiple influenza virus strains. The trial will assess whether receiving M-001 as a prime can help generate enhanced immune responses to a boost vaccination with a licensed seasonal influenza vaccine.

A truly universal influenza vaccine would represent a groundbreaking advance in the fight against influenza. Although we cannot predict when a more broadly protective influenza vaccine

would be publicly available, we expect that progress toward that goal will occur in iterative and progressive steps. NIAID-supported research already has produced promising results. However, we anticipate that it will require significant scientific effort, and multiple refinements along the way, to achieve long-lasting, broadly protective vaccines that can be used in all populations. As we develop such vaccines, promising candidates will need to be evaluated over several influenza seasons to determine the extent and durability of the protection that they induce.

#### *Improving Current Influenza Vaccines*

Concurrent with efforts to develop a universal influenza vaccine, NIAID supports the development of flexible vaccine manufacturing processes, including the use of molecular biological techniques, to help shorten manufacturing times and increase production efficiency for current and future influenza vaccines. NIAID and industry partners are investigating recombinant DNA manufacturing techniques that could be rapidly mobilized when pandemic viruses emerge. In addition, NIAID has supported studies of improved vaccine strain selection and optimized high-yield vaccine strains as part of the Seasonal Influenza Vaccine Improvement (SIVI) initiative, an interagency collaboration launched in 2016. The SIVI initiative builds upon the success of the Influenza Vaccine Manufacturing Improvement (IVMI) initiative, a collaboration with ASPR/BARDA, CDC, FDA, and vaccine manufacturers. The SIVI initiative focuses on approaches to maintain the effectiveness of seasonal influenza vaccines in years when circulating viral strains have drifted by mutating.

In addition, NIAID has supported the development of a new test that can be used to measure the amount of antigen – the substance that generates an immune response – in vaccines to enable a rapid vaccine response during an influenza outbreak or pandemic. The VaxArray Influenza

Pandemic Hemagglutinin test is a new immunoassay for seasonal and pandemic influenza vaccines that can identify multiple HA subtypes, including H5, H7, and H9. This assay represents an improvement over current tests because it can be deployed rapidly to determine and monitor the potency of a greater number of vaccine formulations, such as adjuvanted vaccines and dose-sparing vaccine preparations.

#### *Pandemic Vaccine Approaches*

For decades, NIAID has supported research to prepare for the possible emergence of pandemic influenza. NIAID, in collaboration with BARDA, has evaluated candidate vaccines against pandemic influenza viruses such as the 2009 H1N1 and potential pandemic influenza viruses including H5N1 and H7N9. In the last five years, NIAID has supported 10 clinical trials enrolling more than 3,000 volunteers to assess the safety and immunogenicity of candidate pandemic influenza vaccines. These trials were conducted through the NIAID Vaccine and Treatment Evaluation Units (VTEUs), a longstanding clinical trials network for rapid testing of candidate vaccines and therapeutics. Several of the vaccines also were evaluated for use in special populations such as children and older adults. The VTEUs currently are conducting two Phase II clinical trials of a new vaccine to protect against emerging H7N9 influenza virus strains. The trials are now enrolling volunteers at sites across the United States to test the vaccine's immunogenicity and safety at different dosages and treatment schedules. The studies also will evaluate whether a product called an adjuvant given together with the vaccine boosts the immune response of people receiving the vaccine. In addition, NIAID intramural scientists are conducting clinical studies of prime-boost vaccine regimens for swine (H1) and avian (H7) influenza



viruses, and collaborating with industry and BARDA to develop live, attenuated vaccines against influenza viruses with pandemic potential.

### **Influenza Diagnostics**

NIAID supports the development of influenza diagnostics with improved speed, accuracy, and usability in settings where patients seek medical care. NIAID is helping to develop molecular diagnostic platforms capable of quickly distinguishing between seasonal strains. For example, a rapid molecular test system developed with longstanding NIAID support was recently cleared by the FDA to accurately distinguish influenza A from influenza B in nasal swab specimens. NIAID also supports the development of clinical assays to determine whether influenza virus strains are sensitive to neuraminidase inhibitors – drugs such as Tamiflu that can lessen the duration and severity of illness as well as potentially prevent infection in close contacts.

### **Antiviral Therapies for Influenza**

Antiviral therapies for influenza are important tools in treating and preventing complications of influenza infection. However, the emergence of resistance to existing antiviral medications highlights the need for additional treatment options. NIAID supports research to develop broad-spectrum antiviral drugs and other novel influenza therapeutics, several of which have advanced to clinical trials. For example, NIAID has furthered the development of RNA polymerase inhibitors, peptide inhibitors, and next-generation neuraminidase inhibitors. NIAID also is developing monoclonal antibodies against the influenza HA protein, which facilitates the attachment of the virus to respiratory tract cells. Antibodies that bind to HA potentially could block the interaction between the virus and human cells and thus mitigate influenza disease.

Several of these antibodies are currently in Phase II clinical trials, including a novel monoclonal antibody targeting the stem of the influenza HA protein. In addition, NIAID has launched three clinical trials to assess the effectiveness of novel influenza therapeutics in high-risk populations. These therapeutics include human plasma containing high levels of anti-influenza antibodies, concentrated immunoglobulin with high levels of anti-influenza antibodies, and a combination of three licensed influenza antiviral drugs.

### **Conclusion**

NIAID has a long history of comprehensive and cutting-edge influenza research to develop better diagnostics, therapeutics, and vaccines. Sustained support of NIAID's basic, translational, and clinical influenza research will generate the knowledge needed to reach the goal of safe and effective influenza vaccines that provide durable protection against multiple strains of influenza virus and help us prepare for the next potential pandemic. NIAID will continue to collaborate with government, academic, and industry partners to develop improved tools to prevent, diagnose, and treat influenza infection. Importantly, NIAID will use its new Strategic Plan for a Universal Influenza Vaccine to guide future investments in influenza research to accelerate progress toward broadly protective influenza vaccines.

**Hearing of the House Energy and Commerce, Oversight  
and Investigations Subcommittee**

# **The Role of the National Institutes of Health in Research Addressing Seasonal and Pandemic Influenza**

31

**Anthony S. Fauci, M.D.**

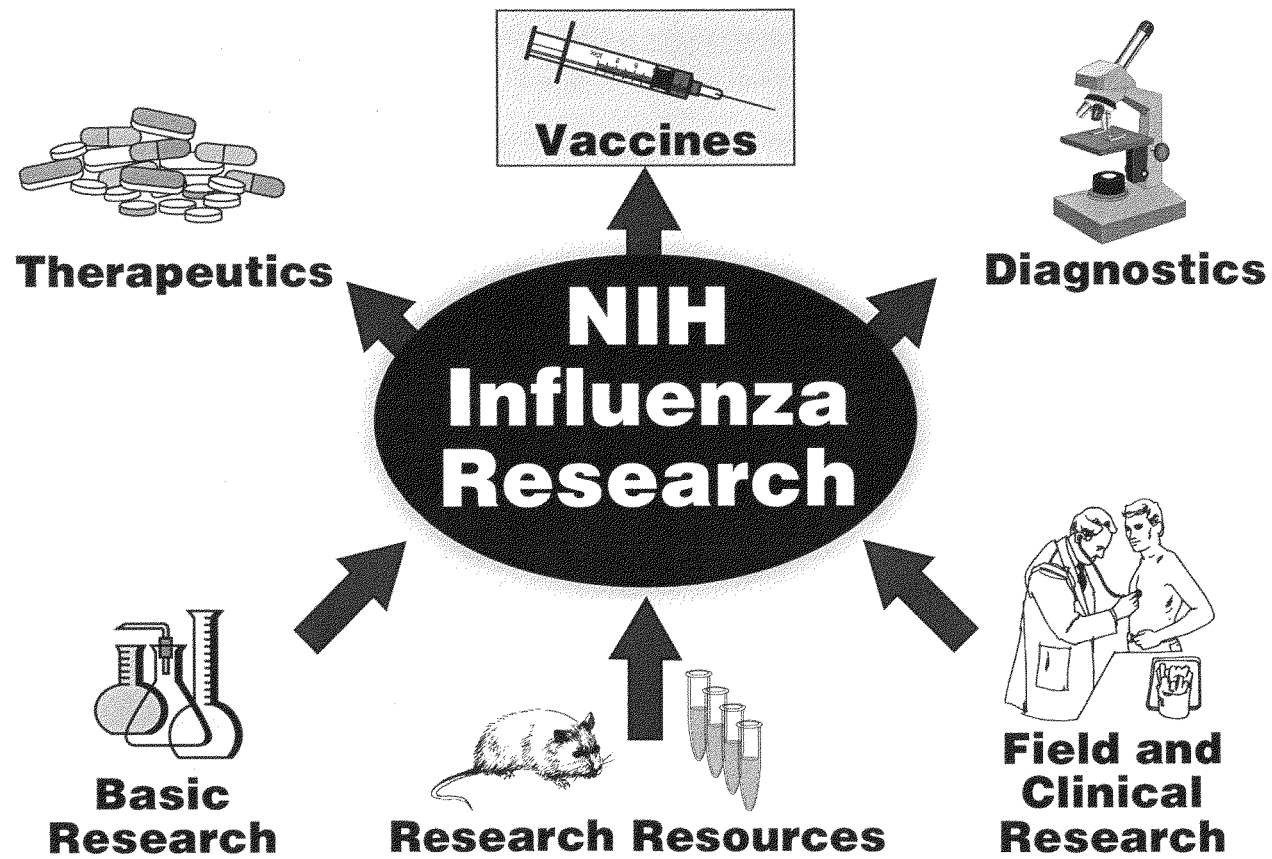
**Director**

**National Institute of Allergy and  
Infectious Diseases**

**National Institutes of Health**

**March 8, 2018**





- **Current seasonal influenza vaccines are not consistently effective**
- **Pandemics do occur and response after the fact is not effective**
- **“Chasing after” potential pandemic outbreaks (pre-pandemic viruses) is costly and ineffective**

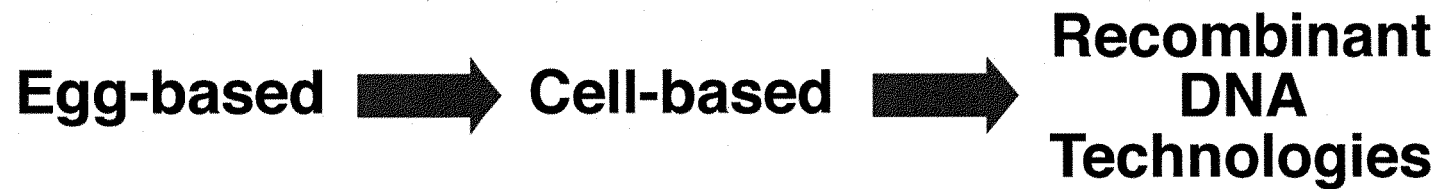
## **Major Challenges in Influenza Vaccinology**

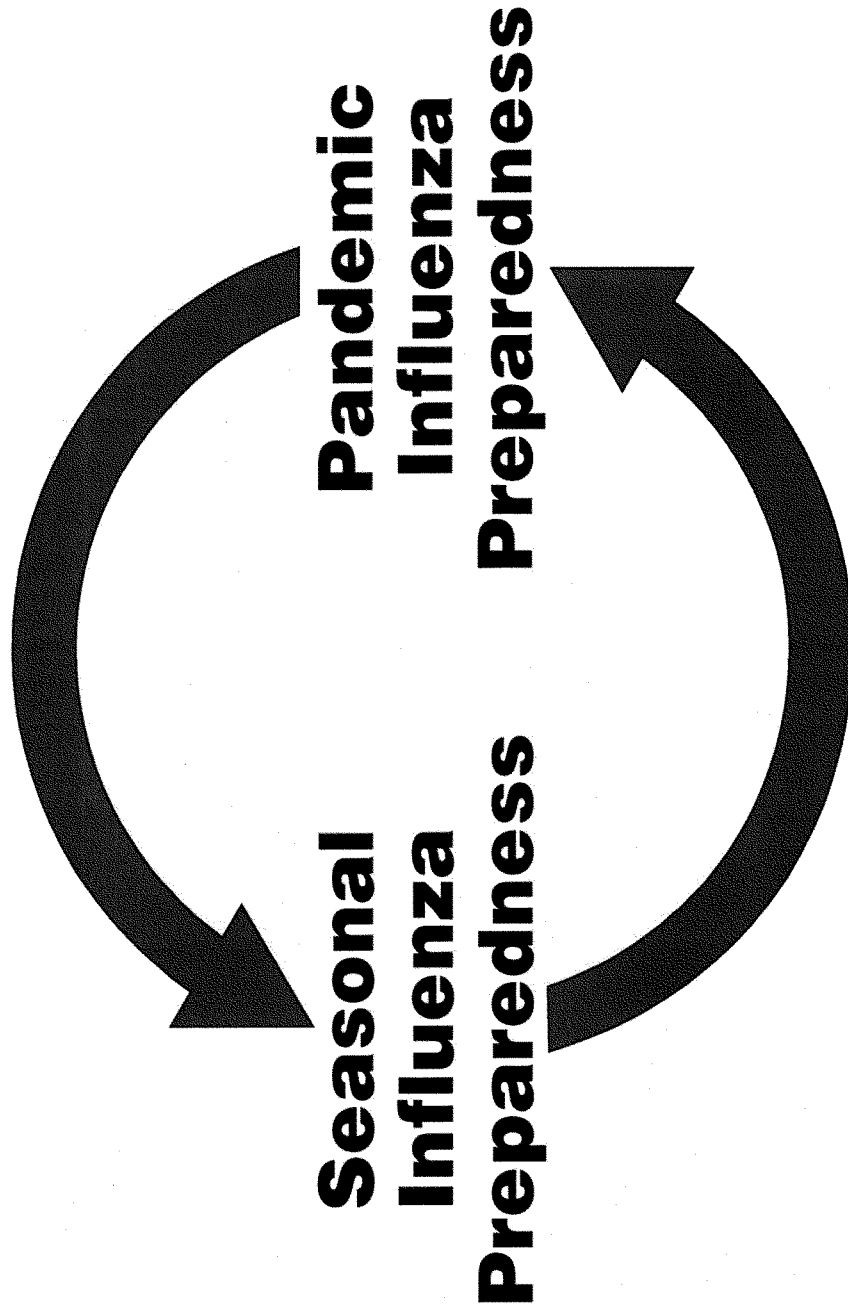
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- **Improve efficacy of current influenza vaccines**
- **Improve production of influenza vaccines – egg-based vs. cell-based vs. recombinant DNA technology**
- **Develop universal influenza vaccines for broad coverage**

## **Evolution of Technologies for Influenza Vaccines**

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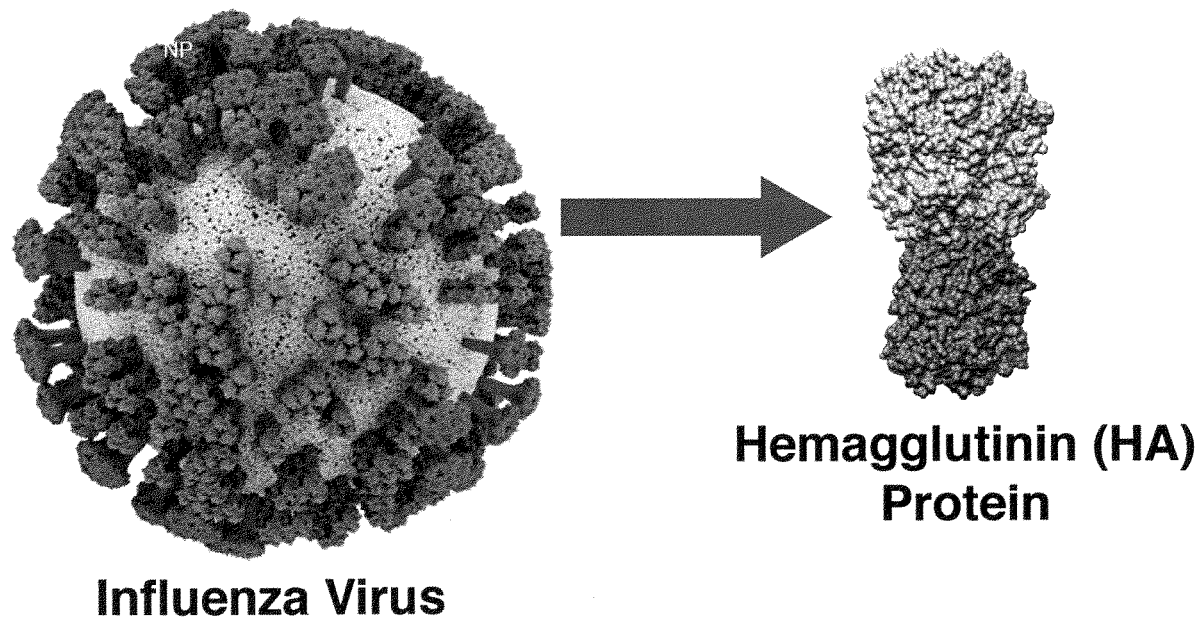
Number 1

# **Chasing Seasonal Influenza – The Need for a Universal Influenza Vaccine**

CI Paules, SG Sullivan, K Subbarao, and AS Fauci

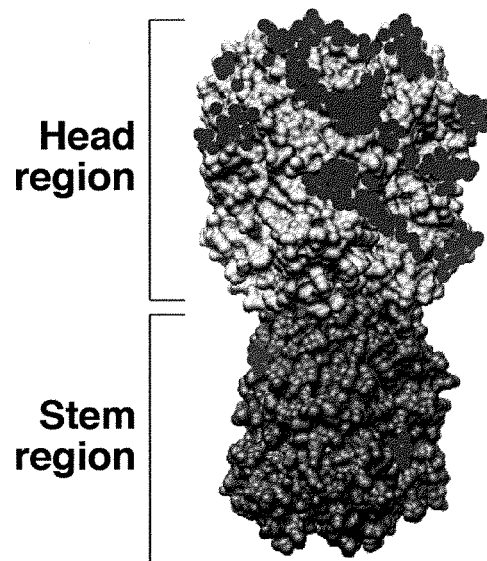
## **Hemagglutinin Protein: Major Target of Influenza Vaccines**

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# Influenza A Hemagglutinin (HA)

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## Head region

- Target of current influenza vaccines
- Differs among influenza strains
- Many mutations (●) each season

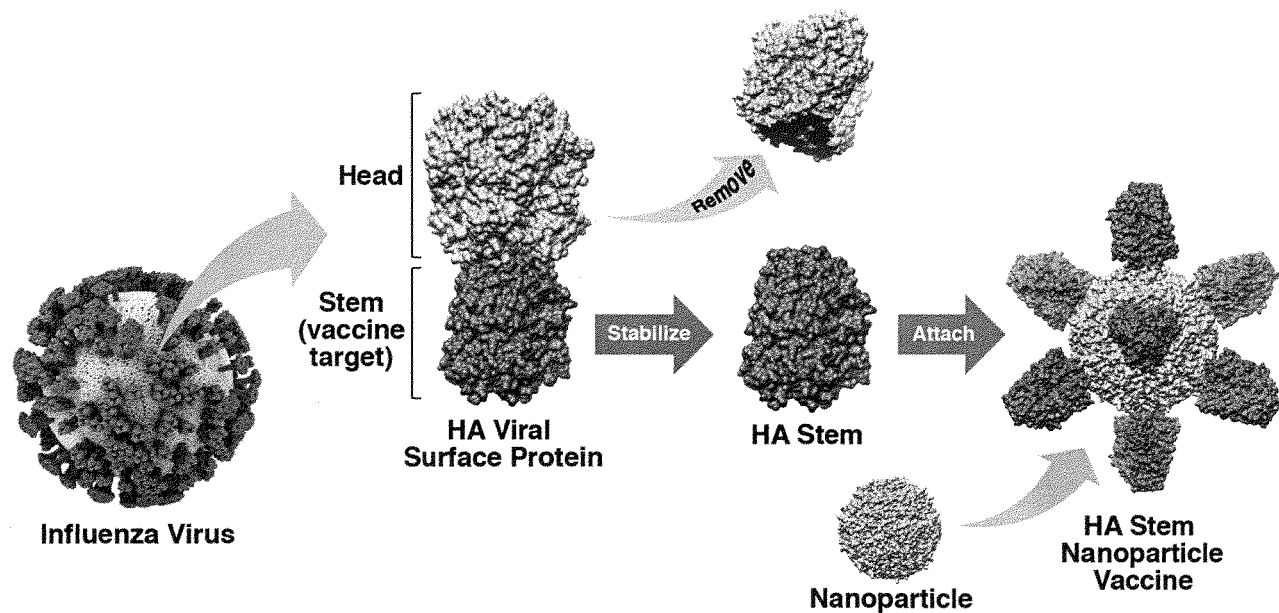
## Stem region

- Target of universal influenza vaccines
- Similar among influenza strains
- Few mutations each season

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# Representative Approach to the Development of a Universal Influenza Vaccine

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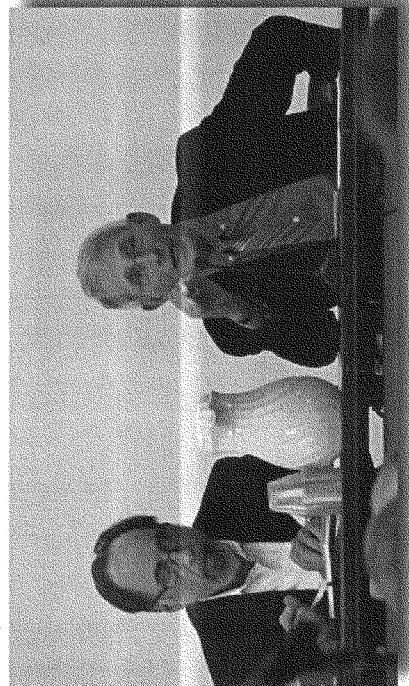
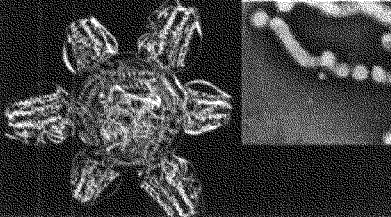
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**Pathway to a Universal  
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June 28-29, 2017

5601 Fishers Lane Conference Center  
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**Immunity**

October 17, 2017  
Volume 47, Issue 4

**The Pathway to a  
Universal Influenza  
Vaccine**

CI Paules, HD Marston, RW Eisinger, D Baltimore,  
AS Fauci

Published online  
February 28, 2018



# The Journal of Infectious Diseases

## **A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases**

**EJ Erbeling, D Post, E Stemmy, PC Roberts, A Deckhut Augustine,  
S Ferguson, CI Paules, BS Graham, AS Fauci**

Mr. HARPER. Thank you very much for that testimony.

Dr. Bright, we'll now recognize you for 5 minutes for the purposes of your opening statement.

#### **STATEMENT OF RICK BRIGHT**

Dr. BRIGHT. Great. Thank you.

Chairman Harper, Ranking Member DeGette, and distinguished members of this committee, thank you for the opportunity to speak with you today on behalf of our Assistant Secretary for Preparedness Response, the ASPR, to discuss influenza and progress towards the development and availability of effective flu vaccines.

I'm Rick Bright, the Director of the Biomedical Advanced Research and Development Authority, known as BARDA, and also the Deputy Assistant Secretary for Preparedness and Response.

ASPR's mission is to save lives and protect Americans from 21st-century threats. BARDA is a component of ASPR that was created to ensure that we have medical countermeasures to protect people from the dire threats we face as a nation. And make no mistake, influenza is one of the most dangerous of those threats.

BARDA was established and empowered with special authorities in the Pandemic and All Hazards Preparedness Act. Guided by a national strategy on pandemic influenza and largely funded through supplemental appropriations, we have proven what can be done when the Government is able to hire the best people, work with the best partners, and remain focused on the strategic fight against influenza. We have shown that the BARDA model works.

With our industry and our Federal partners, BARDA has achieved 34 approvals from the FDA for drugs, vaccines, and diagnostics against a wide range of threats. We have increased domestic flu vaccine capacity over tenfold in world-class production facilities. We have shortened the vaccine response time with modern technologies.

And we have diversified vaccine production platforms, most of that right here in America. No one can rival BARDA's success in expanding capacity and pushing new products to the marketplace. We are proud of these new flu vaccines and the adjuvants now being produced in Pennsylvania, North Carolina, Connecticut, and New York. These include the world's first recombinant flu vaccine and the world's largest cell-based vaccine production facility.

And we are not done yet. Everything that BARDA and our partners have done and accomplished for pandemic influenza can make our seasonal influenza vaccines better and more responsive to the ever-changing virus. Building on our success, we are poised and we are partnered to make better flu vaccines available right now.

Most vaccines today are still made in eggs. Although the process is optimized for efficiency, it has not changed much for decades, and it is no match for a rapidly changing virus. Cell- and recombinant-based technologies are now used to make licensed vaccines, and they offer speed and greater flexibility and may even be more effective than traditional egg-based vaccines.

Despite these advantages, marketplace competition and limited domestic production capacity have largely kept these approaches on the shelf, representing only a fraction of the seasonal vaccine on the marketplace today.

There are actions to improve influenza vaccines now that can produce dramatic near-term benefit in parallel with the long-term efforts being undertaken across the Government to develop a universal flu vaccine. To make better, faster flu vaccines now, we propose, in collaboration with our industry partners, to take the following steps to improve the effectiveness of our existing vaccines:

First, we must expand domestic capacity of the cell- and recombinant-based vaccines. Second, we must enhance their effectiveness with the addition of adjuvants or higher doses of antigen. Third, we need to conduct clinical trials to expand their use in all age groups. And, finally, we need to continue modernizing the vaccine production processes for speed and flexibility.

While we are grateful for the supplemental funding that disrupted the status quo and fueled our progress, those funds have been fully obligated. To win this battle, it is critical that we sustain these hard-won gains and we implement these steps to reduce the threat we face every year from influenza.

And the near-term vaccine improvement activities are only one piece of the puzzle. Equally important is the ongoing work funded by BARDA to develop diagnostics that can detect influenza sooner as well as more effective drug treatment options to treat sick people. These priorities, combined with improved vaccines, represent a comprehensive approach to protecting the Nation and the world against influenza.

Together with our Federal and our industry partners, we have made tremendous progress. However, the threat remains. We stand at a unique moment in time, where we have tools and capabilities to dramatically enhance our fight against influenza. I look forward to working with this panel, your committee, and congressional colleagues.

Thank you for the opportunity to present to you today.

[The prepared statement of Dr. Bright follows:]





**Written Testimony  
House Committee on Energy and  
Commerce, Subcommittee on Oversight  
and Investigations**

**Examining U.S. Public Health  
Preparedness for and Response Efforts to  
Seasonal Influenza**

*Statement of*

**Rick Bright, Ph.D**

Director, Biomedical Advanced Research and Development Authority  
Deputy Assistant Secretary For Preparedness and Response



For Release upon Delivery  
Expected at 10:00 a.m.  
March 8, 2018

**Introduction**

Chairman Harper, Ranking Member DeGette, and distinguished members of the committee, thank you for the opportunity to testify on behalf of the Assistant Secretary for Preparedness and Response (ASPR) to discuss the current influenza season and efforts to develop appropriate and effective medical countermeasures. I am Dr. Rick Bright, Director of the Biomedical Advanced Research and Development Authority (BARDA) and Deputy Assistant Secretary for Preparedness and Response within ASPR.

Today, I will provide background on the unique role of ASPR and BARDA in influenza preparedness, describe the progress made in preparing for an influenza pandemic, discuss the steps we can take now to support better and faster vaccine technologies, and highlight advancements in other medical products needed to mount an effective influenza response.

**The Influenza Threat – Seasonal and Pandemic**

Influenza has long posed a serious threat to human health. Seasonal influenza occurs every year, leading to hospitalizations and deaths. Because influenza viruses mutate as they traffic and reassort among birds, swine, and humans, achieving protection against seasonal influenza viruses is a significant challenge. In addition, because of the quickly changing nature of the virus and the potential for a pandemic, we have to act swiftly to develop effective medical countermeasures and make products available to limit spread. In the last decade, we have been reminded how complex the management of seasonal and pandemic influenza is. Challenges include supporting preparedness efforts across our healthcare system, developing and

manufacturing effective vaccines quickly, and mitigating the impact of the virus through development of diagnostics and antivirals. As a reminder, recent novel influenza outbreaks of significance include:

- The H1N1 pandemic of 2009-2010;
- The emergence of seasonal H3N2 virus variants in 2012 in the Midwest primarily affecting children; and,
- The emergence of H7N9 avian influenza viruses in China in 2013 that were highly virulent for humans, causing repeated outbreaks including the largest outbreak in 2017 of a new variant of the H7N9 virus that required development of a new vaccine.

It is important to note that our approaches to seasonal and pandemic influenza are inextricably interwoven; what we do in one area directly impacts the other. This holds true for preparedness efforts as well as medical countermeasure development and manufacturing capabilities. For example, expanding the domestic manufacturing capacity for pandemic response enabled manufacturers to have the capacity to include an additional strain in the seasonal vaccine—moving from three strain (trivalent) to four strain (quadrivalent) seasonal vaccines for better coverage. This increased production capacity and also supported the U.S. policy to expand influenza vaccination recommendations to include all age groups, ensuring sufficient supply of vaccine would be available to everyone who needs it.

#### **What is ASPR?**

ASPR has a central role in influenza preparedness. When ASPR was originally established by Congress a decade ago, the objective was to create “unity of command” by consolidating all federal public health and medical preparedness and response functions under the HHS Secretary, and by establishing the ASPR as the Secretary’s principal advisor on these matters. This approach was modeled on the Goldwater-Nichols Act that created the Department of Defense (DoD) combatant commands; the impetus was the fragmented response to Hurricane Katrina in 2005 and concerns about an H5N1 influenza pandemic.

ASPR’s mission is to save lives and protect Americans from 21st century health security threats. ASPR is, in effect, the national security mission manager for HHS. As such, on behalf of the Secretary of HHS, ASPR leads the federal public health and medical, preparedness, response and recovery to disasters and public health emergencies, in accordance with the National Response Framework (NRF) and Emergency Support Function (ESF) No. 8, Public Health and Medical Support. It is ASPR’s responsibility to coordinate the nation’s medical and public health capabilities to help Americans during such events, whatever their cause. ASPR also coordinates with other components of HHS with respect to HHS’s role in ESF No. 6, Health and Social Services, and HHS’s lead role as the coordinating agency with respect to the Health and Social Services Recovery Support Function.

ASPR, in partnership with other HHS agencies, works to enhance medical surge capacity when needed during disasters by organizing, training, equipping, and deploying federal public health and medical personnel and providing logistical support for federal responses to public health emergencies. ASPR also supports readiness and preparedness efforts at the state and local level

by coordinating grants to support capabilities across the nation's healthcare infrastructure and carrying out drills and operational exercises. ASPR oversees advanced research, development, and procurement of medical countermeasures (e.g., vaccines, medicines, diagnostics, and other necessary medical supplies) against biomedical, chemical, radiological and nuclear agents and pandemic or epidemic diseases and coordinates the stockpiling of such countermeasures.

#### **What is BARDA?**

BARDA is a component of ASPR. Congress established BARDA to bridge the so-called "valley of death" in late-stage development of medical countermeasures where many products historically languished or failed due to a limited commercial market incentive. Generally, the development of an effective medical countermeasure can take over 10 years and cost over \$1 billion. By using flexible, nimble authorities, multi-year advanced funding, strong public-private partnerships, and cutting edge expertise, BARDA has successfully pushed innovative medical countermeasures, such as vaccines, drugs, and diagnostics, through advanced development to stockpiling and Food and Drug Administration (FDA) approval or licensing.

In the last decade, BARDA's strong partnerships with 190 biotechnology and pharmaceutical companies, U.S. government partners, and academic institutions have led to 34 medical countermeasures approved or licensed by the FDA. BARDA has supported the development of 27 medical countermeasures against Department of Homeland Security (DHS)-identified national security threats through Project BioShield, including products for smallpox, anthrax, botulinum, radiologic/nuclear emergencies, and chemical events. Fourteen of these products

have been placed in the Strategic National Stockpile and are ready to be used in an emergency. BARDA has also supported the development and production of 23 influenza vaccines, antiviral drugs, and diagnostics; some of these were used in the 2009 H1N1 pandemic, stockpiled to enhance preparedness for H5N1 and H7N9 influenza outbreaks or pandemics, and some were licensed for seasonal influenza and are entering the marketplace.

BARDA focuses on advanced development, which includes critical steps needed to transform a promising candidate into a product that is ready to use safely when a crisis hits. These steps include: optimizing and validating commercial scale manufacturing processes; optimizing product formulations, storage, product longevity and effectiveness; creating, optimizing, and validating assays to assure product integrity; and, conducting late-stage clinical safety and efficacy studies.

#### **Better and Faster Influenza Vaccines Right Now**

BARDA has always been driven by the strategy to make more, safer, faster, and better influenza vaccines. With benefits to both pandemic and seasonal influenza preparedness and response, BARDA has prioritized partnering with industry partners to build domestic vaccine manufacturing infrastructure, and develop and license better and faster manufactured influenza vaccines. With supplemental funding from Congress over the last decade, BARDA has invested heavily in increasing the domestic capacity for monovalent vaccine antigen production—from approximately 60 million doses to 600 million doses.

BARDA also established the first and largest pre-pandemic influenza vaccine stockpile in the world, one that could, if necessary, vaccinate tens of millions in the event of H5N1 and has advanced the science of antigens and adjuvants through unique programs. The stockpile and rapid response capability is a true national asset that not only provides vaccine to America's first responders and critical workforce, but also provides each vaccine manufacturer that holds a US license with valuable lead time to develop vaccines against influenza viruses that pose the greatest risk to becoming a pandemic virus. This asset also allows for BARDA, industry and HHS partners to develop reagents and conduct clinical studies to understand the science about each of these vaccines. This lead time and advance work saves a tremendous amount of time during the start of a pandemic, therefore leading to the more rapid availability of vaccine and ultimately to saving lives. While this represents a significant accomplishment, and a success of the BARDA public-private partnership model, there is more to be done to ensure that the most effective vaccines are available when and where we need them.

Since the 2009 influenza pandemic, BARDA has made significant progress in partnering with cutting edge companies to develop novel manufacturing technologies that offer the potential to provide more effective influenza vaccines.

The traditional technology for manufacturing influenza vaccines is egg-based. Although this method has been optimized for efficiency, it has not fundamentally changed since the 1940's, and it is still the predominant method of vaccine production for the commercial market today. Recognizing the need to improve the robustness and responsiveness of our vaccine manufacturing technology, BARDA first began supporting the development of six different cell-

based manufacturing technologies in 2006 and three different recombinant manufacturing technologies in 2009. As a result of these investments, a cell-based influenza vaccine (Fluceivax®) was developed. Fluceivax was licensed by the FDA in 2012, and is now produced by Seqirus in Holly Springs, NC and can now be administered to individuals four years and older. In 2013, the FDA licensed the first recombinant influenza vaccine (Flublok®) that can be given to people over 18 years of age. This vaccine was developed by Protein Sciences Corporation which was recently acquired by Sanofi Pasteur. BARDA also supported several companies to develop influenza vaccine adjuvanted to enhance the effectiveness of the seasonal vaccine and to reduce the overall amount of vaccine antigen needed in a dose as a way of stretching a limited supply to protect more people faster during a pandemic. The first pre-pandemic vaccine adjuvanted was developed by GSK, which was soon followed by achieving licensure of a season influenza vaccine adjuvant for adults over age 65.

These cell-based and recombinant technologies offer the potential to provide more effective vaccines than those produced in eggs, more quickly, and with flexibility to rapidly shift to keep pace with changes in the virus. However, due to marketplace competition, such as a current inability to differentiate cell-based and recombinant technologies in the market, and limited domestic production capacity, during the 2017/2018 influenza season these vaccine technologies represent only 18 percent and 3 percent, respectively, of the total vaccine available. Investments in next-generation manufacturing processes to maximize the scale, efficiency and speed of cell-based and recombinant technologies, as well as investments in clinical studies needed to expand age indications and validate potential benefits of these vaccines, including the potential to have more effective vaccines that are not vulnerable to adapting human vaccine viruses to grow



efficiently in chicken eggs will help improve preparedness and response for both seasonal and pandemic influenza. In addition, utilizing these flexible manufacturing technologies domestically also improves our capability to rapidly produce other critical medical countermeasures for other threats.

There are significant strides that can be made to improve the effectiveness of our existing vaccines in preparation for the long-term vision of an ultimate universal influenza vaccine. Leveraging the successful development and licensure of both recombinant and cell-based influenza vaccines, we should:

- 1) Continue to expand the domestic capacity of cell-based and recombinant influenza vaccines;
- 2) Explore ways to enhance their effectiveness, such as through the addition of adjuvants and higher doses of vaccine;
- 3) Conduct clinical trials in support of applications to expand their licensed indications for all age groups; and,
- 4) Fully integrate manufacturing process improvements to realize efficiencies to increase flexibility and robustness while reducing response time and establishing a 21<sup>st</sup> century foundation for next generation vaccines.

Moreover, to improve influenza vaccines now, we must modernize and harmonize the end-to-end process of vaccine production, to completely incorporate new technologies to decrease the time needed to produce vaccines that are ready for administration, and increase efficiency and flexibility. We must also work closely with our partners in industry and at the FDA to continue

to explore modern methods of continuous manufacturing of vaccine that will provide added flexibility and response capabilities matched to the rapid changes we know so well with influenza. BARDA will continue to invest in sustaining the overall domestic influenza vaccine manufacturing capacity to ensure vaccines can be produced and accessed quickly when needed to protect health in a pandemic. Emergency supplemental funding supported the work to increase this domestic resource, in recognition of the urgent need to have U.S.-based response capabilities, and we must sustain these hard-won gains.

#### **Advancing Other Medical Products Needed for Effective Influenza Response**

While vaccination is the best way to prevent influenza infection, every year, and especially in the event of a pandemic, a large number of individuals will nevertheless become ill and will need urgent treatment. There is an ample supply of antiviral drugs, including pediatric formulations, for this influenza season. However, continued development of novel antivirals is essential to provide additional treatment options if drug resistance emerges to our only class of currently FDA-approved and CDC-recommended influenza drugs. BARDA is committed to the development of novel treatments for people infected with influenza. Last year, BARDA utilized Other Transactional Authority to forge flexible, portfolio-based public-partnerships with Janssen, and Regeneron to address this critical need.

Early information on influenza infection is critical for proper treatment, and can help reduce the spread of disease. The time needed to effectively access, administer, and receive results from current diagnostic tests often exceeds the window of opportunity for optimal treatment; current influenza drugs are most effective when taken within the first 48 hours of symptom onset.

Therefore, BARDA is partnering with companies and researchers to develop new influenza diagnostics. Our goal is to develop in-home and wearable diagnostics to inform and empower patients to take responsible actions towards earlier treatment and non-pharmaceutical approaches to reduce the severity of their illness, reduce the spread of disease, reduce overall health care costs and to save lives. An in-home or wearable diagnostic would have a positive impact by providing early, actionable information to the patient.

### **Conclusion**

Influenza and other emerging infectious diseases with pandemic potential continue to mutate, evolve, and infect animals and humans, posing continued significant threats to global public health and to the security of the United States. Together with our Federal and industry partners, ASPR and BARDA have made huge progress towards pandemic influenza preparedness. Our Nation must continue to invest in domestic pandemic preparedness efforts and work with key global partners to prepare for, prevent, detect, and respond to emerging pandemic threats. Building on a decade's worth of progress, partnered with industry, the time is right to make better seasonal and pandemic influenza vaccines, antivirals, and diagnostics widely available. BARDA has a unique responsibility in supporting advanced research, development, and procurement of pandemic influenza medical countermeasures. While the promise and advantages of universal influenza vaccines is an elusive but highly worthy goal, led by our colleagues at NIH, the near term threat of influenza demands that we work right now to make influenza vaccines better and faster, and we ensure that diagnostic tools and antiviral treatments are also available to save lives. Now is the time to act. Thank you for your time, and I look forward to your questions.

Mr. HARPER. Thank you very much.

The Chair now recognizes Scott Gottlieb for 5 minutes for the purposes of his opening statement.

#### STATEMENT OF SCOTT GOTTLIEB

Dr. GOTTLIEB. Thank you, Mr. Chairman and Ranking Member DeGette and members of the subcommittee. Thank you for the invitation to testify on our response to the 2017–2018 seasonal flu.

This flu season has been particularly hard. I agree with my colleagues that investing in and working towards a universal flu vaccine is crucial. Unfortunately, given where we are today in the development process, that reality is still many years off.

While we should continue to focus on the discovery of a new breakthrough vaccine, we must also consider what immediate and intermediate steps we can take to enhance the production of existing licensed vaccines and what should be done to invest in advanced domestic manufacturing to ensure that new and existing technologies are scalable so that manufacturers meet domestic and global demand.

There have been successes in developing alternatives to egg-based vaccines, such as cell-based and recombinant technologies, in part because of the collaborations and work by BARDA. However, despite these advances in vaccine development, the majority of manufacturers are still continuing to produce egg-based vaccines.

There are reasons for this. The egg-based process works, and the vaccines are safe and effective. But, even more so, it would require an enormous investment to fundamentally change manufacturing.

However, we believe it's worth better understanding the potential of cell-based or recombinant alternatives. Some studies have found that cell-based or recombinant vaccines could be more efficacious than egg-based vaccines, but more data and analyses are needed.

As one step to better understanding the differences between egg-based and cell-based technologies, we're using CMS data to compare Medicare patients that received the cell-based vaccines to those who received an egg-based vaccine to determine which vaccine was more effective in that population.

As we consider greater investments in alternative vaccine development processes, it's important to note, however, that there are also challenges with these new cell-based approaches. To help address these challenges, FDA is working to help develop more effective cell lines that can be better scaled through continuous manufacturing. We're also looking at how we develop a more robust recombinant vaccine manufacturing process to increase yield while reducing cost.

Continuous manufacturing holds great promise for both cell-based and recombinant vaccines because supply could be more easily ramped up on short notice. This would allow us to more rapidly address newly emerging strains or strain drift. Getting all the necessary preparatory work done is one limiting step of the egg-based processes.

The FDA can help industry make investments in these new manufacturing technologies and facilitate such a transition. We need to develop a science-based framework that includes the regulatory

tools and guidelines for products to be developed in these systems and to be properly evaluated. And, ultimately, our investment will provide regulatory clarity for this kind of new technology. That regulatory framework can increase the efficiency and reduce the cost of transitioning to this kind of new cell-based and recombinant product development manufacturing.

More immediately, as we prepare for next year's flu season and analyze the data from this year, we're trying to better understand why this year's vaccine was less effective against H3N2. At FDA's recent advisory committee meeting, the data presented continued to suggest that the strains selected for the 2017 and 2018 vaccines and used by manufacturers reasonably match the circulating strains. This includes the H3N2 strain.

Although adapting circulating virus strains from manufacture can lead to differences between the circulating strains and the one used for manufacturing and although those changes could affect vaccine effectiveness, the case this year is likely to be much more complex.

And this year is not the first time we've seen vaccines be less effective against H3N2. Recent flu vaccines have proven, on average, to be only about 33 percent effective against the H3N2 viruses. Given this, we're looking at several factors to better understand why effectiveness tends to be lower against this strain.

As we continue to invest in the future of manufacturing and vaccine technology, we also need to remember the importance of simply ensuring that more people get vaccinated with available vaccines each flu season. And we also must work hard to ensure that products used to treat the flu, including antivirals and IV saline, are available and that we take steps to address any potential shortages.

As always, FDA remains committed to communicating and sharing updates with the public about all aspects of our flu response. And I look forward to answering your questions today. Thank you.

[The prepared statement of Dr. Gottlieb follows:]

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**TESTIMONY  
OF  
SCOTT GOTTLIEB, M.D.  
COMMISSIONER OF FOOD AND DRUGS  
FOOD AND DRUG ADMINISTRATION  
DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**BEFORE THE  
SUBCOMMITTEE ON OVERSIGHT AND INVESTIGATIONS  
COMMITTEE ON ENERGY AND COMMERCE  
U.S. HOUSE OF REPRESENTATIVES**

**“EXAMINING U.S. PUBLIC HEALTH PREPAREDNESS FOR  
AND RESPONSE EFFORTS TO SEASONAL INFLUENZA”**

**MARCH 8, 2018**

**RELEASE ONLY UPON DELIVERY**

### **Introduction**

Chairman Harper, Ranking Member DeGette, distinguished members of the Subcommittee, I am Dr. Scott Gottlieb, Commissioner of the U.S. Food and Drug Administration (FDA or the Agency). Thank you for the opportunity to be here today to discuss FDA's role in the highly collaborative effort in preventing influenza through vaccination in the United States.

Influenza (flu) is a major public health concern. Annually, flu causes illness in a substantial proportion of the U.S. population and may result in serious complications, including events leading to hospitalization and death. Influenza viruses are highly unpredictable. Each year, they can present new challenges for vaccine manufacturers, public health agencies, providers, and patients. The current flu season has been especially challenging, with widespread activity that has affected all fifty states, resulting in a record number of hospitalizations.

Although healthcare providers are still busy taking care of people with influenza this season, essential work has started on the production of next year's influenza vaccines. As this process moves forward, FDA is committed to continuing to examine the factors that impacted vaccine effectiveness from this season. Our goal is to work with other public health agencies to ensure that vaccines produced for the next season will have the greatest chance of being effective in preventing influenza.

Influenza viruses continually undergo changes in their genetic makeup and the resulting proteins that interact with the immune system. These changes can occur from one season to the next. They can also occur within the course of an influenza season. Unlike other vaccines, the composition of influenza vaccines must be periodically updated so that they are effective against the predominant circulating viruses anticipated in the upcoming influenza season. The strains of virus used in vaccine production include two distinct subtypes of influenza A (H1N1 and H3N2) and one (for trivalent vaccine) or two (for quadrivalent vaccine) different lineages of influenza B (B/Yamagata and B/Victoria, which are genetically divergent from each other).

### **A Global Process for Virus Strain Selection**

The process of ensuring the timely availability of influenza vaccine in the United States and elsewhere is a global, year-round process. Each year, the World Health Organization (WHO) convenes technical consultations in February and September to recommend the virus strains for inclusion in influenza vaccines for the Northern and Southern Hemispheres, respectively. FDA participates in both technical meetings. To identify virus strains likely to cause illness during the upcoming influenza season, experts from WHO Collaborating Centers for Influenza (which include the Centers for Disease Control and Prevention (CDC)), the WHO Essential Regulatory Laboratories (this includes FDA's Center for Biologics Evaluation and Research (CBER)), and other influenza and public health experts study recently circulating influenza viruses and recent global disease patterns. In addition, blood samples from individuals receiving the most recent

influenza vaccines are analyzed by the WHO Essential Regulatory Laboratories and WHO Collaborating Centers to determine how well antibodies induced by these vaccines react to recently isolated viruses. After careful evaluation of the antigenic and genetic characteristics of influenza viruses that are circulating and infecting humans across the globe and the ability of current vaccines to protect against these viruses, WHO makes recommendations on the composition of the influenza vaccines for use in the upcoming influenza season.

These recommendations are then reviewed by national vaccine regulatory agencies, such as FDA, and vaccine manufacturers as they consider the vaccine composition for the upcoming season. WHO usually makes its vaccine strain recommendations in February for the upcoming influenza season in the Northern Hemisphere and in September for the upcoming influenza season in the Southern Hemisphere. The recommendations must be made months in advance of the next influenza season. This is to accommodate the time that is required for manufacturing, testing, lot release, and distribution of a very large number of vaccine doses consisting of antigens derived from three or four different influenza virus strains.

#### **FDA's Role and the Manufacturing Process**

WHO recommendations, resulting from the technical consultations described above, provide a guide to national public health authorities and vaccine manufacturers for the development and production of influenza vaccines for the upcoming influenza season. In the U.S., FDA is responsible for regulating vaccines. In this role, FDA brings together public health and influenza disease experts to recommend which influenza virus strains should be included in FDA-licensed vaccines. FDA convenes its Vaccines and Related Biological Products Advisory Committee (VRBPAC) each year, typically in late February or early March and within a few weeks after the WHO consultation on influenza vaccine composition. The meeting to provide recommendations on strain selection for the upcoming 2018-2019 United States influenza season took place on March 1, 2018.

The VRBPAC considers the recommendations made by the WHO regarding the composition of influenza vaccines for the upcoming influenza season in the Northern Hemisphere. The committee also reviews information regarding viruses that have caused human illness in the previous year, how these viruses are changing, and disease trends. CDC and other WHO Collaborating Centers provide most of the information considered in the course of this review. Based on the data available at the time of the meeting, the Advisory Committee makes a recommendation for the composition of influenza vaccines licensed by FDA for use in the United States during the upcoming season.

Influenza viruses that grow well in culture, which have been generated and accepted by WHO collaborating centers, are provided to the licensed vaccine manufacturers to generate the "seed viruses" for manufacturing their influenza vaccines. FDA confirms the antigenic suitability of the manufacturer's seed viruses. The manufacturing demands for influenza vaccines are



substantial. No other routine vaccine is produced, FDA-approved, and distributed every year across the United States within an approximately six-month time frame. The manufacturing timelines are tight and the process of producing influenza vaccines involves many sequential steps and overlapping processes. Even with technologic advancements, each of these steps and processes still requires time to complete. Given the yearly need for an update to the strains included in each licensed flu vaccine, there is limited flexibility in the timelines for influenza vaccine production and availability. There is the possibility that advances in manufacturing, as well as the adoption of different technologies for the production of antigen, can help compress this process and provide greater predictability. Certain technologies could also offer more opportunity to adjust the vaccine closer to the influenza season should a new influenza strain emerge after production has already begun.

Vaccine manufacturers must annually submit to FDA a supplement to their license to include the updated influenza virus antigens in their vaccine. FDA must review and approve a supplement before the updated version of the influenza vaccine containing new virus antigens can be distributed. Manufacturing of each antigen to be included in the vaccines occurs sequentially over several months, usually from December (produced at risk by manufacturers before the strain recommendations are made) until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents that are provided to the vaccine manufacturers and our regulatory counterparts throughout the world. Manufacturers and FDA use these reagents to test the vaccines for potency and identity before FDA approves the new formulation of the licensed seasonal influenza vaccines for U.S. distribution.

The vaccines are formulated into standard dosages, filled and finished by the manufacturers into final containers such as vials, syringes, and sprayers. Manufacturers submit their vaccine testing results, along with samples from each lot, to FDA for “lot release.” As FDA releases lots, the manufacturers can make these lots commercially available throughout the United States.

Typically, FDA approves the updated seasonal influenza vaccines with new labeling by the end of July. Every year, FDA begins working with manufacturers at the earliest stages of influenza vaccine development, and we continue to assist them throughout the production phase. During this period, we engage the companies on technical and manufacturing issues and conduct facility inspections to ensure compliance with good manufacturing practice, as warranted.

#### **2017-2018 Influenza Season**

FDA's VRBPAC met on March 9, 2017, to provide recommendations on the composition of the influenza vaccine for the 2017-2018 U.S. influenza season. During this meeting, the Advisory Committee reviewed and evaluated the surveillance data related to epidemiology and antigenic characteristics of recent influenza isolates, serological responses to 2016-2017 vaccines, and the availability of candidate strains and reagents. The Committee recommended that the trivalent

influenza vaccines for the U.S. 2017-2018 influenza season be produced with the following: an A/Michigan/45/2015 (H1N1) pdm09-like virus, an A/Hong Kong /4801/2014 (H3N2)-like virus, and a B/Brisbane/60/2008-like virus (B/Victoria lineage). The Committee also recommended that quadrivalent influenza vaccines be produced with the above three strains and the following additional B strain: a B/Phuket/3073/2013-like virus (B/Yamagata lineage).

This year, much of the influenza-related illness has been caused by one strain of influenza A called H3N2, with another strain of influenza A called H1N1 and strains of influenza B contributing to lesser extents. CDC recently published the interim estimates of 2017-2018 seasonal influenza vaccine effectiveness in the United States. Overall adjusted vaccine effectiveness for H1N1 and influenza B strains was not too far off from prior seasons at 67 percent and 42 percent, respectively. However, overall adjusted effectiveness for H3N2 influenza was only 25 percent. The effectiveness of the vaccine against H3N2 in children 6 months to 8 years of age was 51 percent, yet the effectiveness in those 65 years and older was only 17 percent. Individuals over 65 years of age always tend to have a lower response rate to influenza vaccine, and improving the response in this age group is one of the challenges that we must address.

Reduced effectiveness of vaccination against H3N2 relative to H1N1 and influenza B has been seen in prior seasons. Scientists at FDA are working with colleagues at other agencies to try to understand the reasons for the difference in the effectiveness of the vaccine against H3N2 relative to the other types of influenza. The work that they are doing includes laboratory and epidemiologic investigation. For example, in trying to understand whether one type of influenza vaccine performs better than another in individuals 65 years of age and older, they are making use of an established collaboration with the Centers for Medicare and Medicaid Services (CMS).

As part of this collaboration, our scientists are looking at the effectiveness of various influenza vaccines in preventing hospitalizations for influenza and treatment for influenza-like illness in four million individuals for whom information is available in the large database regarding what type of influenza vaccine they received. They are using the database to look for differences in effectiveness in those receiving egg-based and cell-based vaccines, as well as differences in effectiveness in those who were vaccinated with standard-dose versus high-dose influenza vaccine and adjuvanted influenza vaccine. The high dose vaccine contains four times as much of the influenza antigen as standard vaccines, and the adjuvanted influenza vaccine contains an ingredient meant to boost the immune system's response to the vaccine. Differences observed in the effectiveness of differently-produced vaccines against H3N2 may offer important insights into why the most widely-used, egg-based vaccines have reduced efficacy against this strain.

### **Progress in Influenza Vaccine Manufacturing**

Despite difficulties inherent in preparing influenza vaccines, we continue to make progress in our preparedness efforts in collaboration with the Biomedical Advanced Research and Development Authority (BARDA), CDC, the National Institutes of Health (NIH), and other stakeholders.

New influenza vaccines have been licensed in recent years, including cell-based influenza vaccines, recombinant protein vaccines, and quadrivalent influenza vaccines. Cell-based and recombinant protein influenza vaccines provide alternatives to the traditional egg-based process of manufacturing, and provide the potential for a faster vaccine manufacturing process. FDA has licensed a cell-based influenza vaccine and a recombinant influenza vaccine. FDA has also licensed quadrivalent vaccines that are intended to protect against two influenza A strains (H3N2 and H1N1) and two influenza B strains. In addition, FDA has approved high-dose and adjuvanted vaccines specifically for the elderly population who can require an adjuvant or higher exposure to antigen in order to develop an adequate immune response to the influenza vaccine.

CDC's surveillance efforts to monitor for circulating influenza strains are more extensive than ever before. These efforts offer the potential for early detection of emerging influenza viruses. The number of candidate vaccine virus strains available to manufacturers has increased greatly over the last few years, providing them with more options to increase vaccine yields. FDA, in conjunction with NIH, BARDA, and CDC, continues efforts to develop high-yield candidate vaccine strains, as well as more modern, faster methods to measure vaccine potency and sterility.

To further address the challenges presented by the constantly changing nature of influenza viruses, scientists in government laboratories, academic institutions, and vaccine manufacturers are working to develop new-generation vaccines that might be longer lasting and provide broader protection against drifted strains. Ultimately, developing a universal influenza vaccine that provides protection against many different strains of flu from year-to-year would be ideal.

However, the reality of such a vaccine is likely to still be many years away. In the meantime, FDA is collaborating with Federal partners and with industry to improve the manufacturing of the current generation of influenza vaccines. Advances in manufacturing, including wider consideration of cell-based manufacturing, continuous manufacturing, and the use of recombinant vaccines, may offer the best near-term opportunity to improve vaccine timeliness and effectiveness. Our scientists are interested in looking at whether advanced manufacturing technologies, including continuous manufacturing of cell-based and recombinant vaccines, could help facilitate much more agile response to changes in influenza strains. Use of continuous manufacturing could also have the added benefit of allowing the rapid scale-up and production of vaccine in the United States within compact manufacturing facilities. The potential benefits of these advancements are also applicable to our ongoing efforts to enhance our nation's preparedness for pandemic influenza.

Although these vaccine development efforts are still in early stages, some may have the potential to increase and broaden protection against influenza. FDA will continue to work with U.S. Government partners, manufacturers, and other stakeholders to facilitate development of new vaccines and identify methods that have the potential to speed the manufacturing process for existing vaccines. Our goal is to better protect the American public, including those at higher risk of complications from influenza such as the very young and the elderly.

#### **Diagnostics and Antivirals**

Finally, I want to highlight FDA's role in approving rapid diagnostic tests and antiviral therapies. Currently, there are 13 rapid flu tests available for marketing in the U.S. These rapid flu tests, which are medical devices, include antigen-based tests and nucleic acid-based tests that are available for use in primary care. To improve the overall accuracy and reliability of flu testing, FDA recently reclassified antigen-based rapid influenza diagnostic tests, which included new performance and testing requirements to demonstrate the ability of a rapid flu test to detect currently circulating viruses. We expect the new requirements to lower the number of misdiagnosed flu infections by promoting the development of new, improved tests that can more reliably detect the virus. This will ensure patients and providers are receiving accurate diagnostic information without reducing access to reliable tests.

Currently there are several antiviral drugs approved for prophylaxis and/or for treatment of acute uncomplicated influenza, and several others in clinical trials. FDA monitors for shortage, safety, and manufacturing issues associated with the available drugs. FDA works closely with developers of antiviral drugs to review and advise on development pathways and clinical trial designs to enhance understanding of the role of these drugs in influenza preparedness and treatment. A major goal is to encourage availability of a variety of treatments that can be shown to benefit a broader range of patient populations and influenza outbreak strains.

#### **Conclusion**

In closing, I would like to assure the Committee that FDA will continue to advance policies and the science to help improve the overall reliability, efficiency, and effectiveness of the vaccine production process. We will apply all the knowledge gained in conjunction with NIH, BARDA, CDC, and other Federal partners as we work together with manufacturers to ensure that the best possible vaccines are available next season to protect against the flu.

Mr. HARPER. Thanks to each of you for your opening statements. And, you know, this is an incredible panel of witnesses that are here today, that cover the entire spectrum of people that are daily dealing with this important issue. So thank you for this time, this education you're giving us.

And so I'm going to recognize myself to ask the first set of questions. And this is for each of you, just for quick responses, if you would just reply to this.

This year has been an especially difficult and severe flu season. A lot of lives have been lost, and many people have been hospitalized. Would you get the vaccine and have your loved ones get it also?

Dr. SCHUCHAT. Yes. I get the vaccine every year and make sure my whole family does.

Dr. FAUCI. Same here. I got the vaccine this year and every year over the last as many years as I can remember, as have my wife and three children.

Dr. BRIGHT. Absolutely.

Dr. GOTTLIEB. Absolutely, sir. I go to the pediatrician with my children, and the pediatrician gives it to me and gives it to them.

Mr. HARPER. That's great.

All right. If you get the flu after getting the flu vaccine, is having gotten the flu vaccine likely to reduce the severity of the illness?

Dr. SCHUCHAT. Yes. There are studies now that have shown reduced severity following immunization even when the disease itself isn't prevented.

Dr. FAUCI. That is true, and that's an important point that many people don't appreciate, because they say, "I did get the flu even though I got vaccinated." What they don't realize, that it is likely—not likely, but it is possible that having gotten the flu without the vaccine would have wound them up in the hospital, particularly if they were someone in the risk groups that are more prone to getting complications.

Mr. HARPER. Dr. Bright?

Dr. BRIGHT. Absolutely. There's data to support that the vaccine, even if it's not the most effective vaccine, still does a lot to reduce the severity of illness and reduce hospitalization.

Dr. GOTTLIEB. I would just echo those statements.

Mr. HARPER. Great.

Now, I've heard some concerns that some individuals are worried that they may get the flu from the flu vaccine. Is that possible?

Dr. SCHUCHAT. No. The flu vaccine cannot cause the flu.

Dr. FAUCI. Very few things that you say are impossible, but this is impossible.

Mr. HARPER. OK.

Dr. BRIGHT. Agreed.

Dr. GOTTLIEB. I agree as well, sir.

Mr. HARPER. That's great. There are those misconceptions out there, that when I had this esteemed group here I wanted to make sure that people realize those important facts going forward.

Dr. Schuchat, if I may talk to you for a moment, this year we've seen a lot of headlines about the flu vaccine's reduced effectiveness. Later, we're going to ask questions about why we likely saw re-

duced effectiveness in the flu vaccine, but, first, however, I want to ask about vaccine effectiveness for children this year.

You had answered the effectiveness of that was 59 percent effective, much better than it was in adults. But why was it more effective on children than it was, say, older adults?

Dr. SCHUCHAT. We don't have all the answers, but there are a couple of possible explanations. One is children's immune response is often better than adults, particularly better than older adults.

A second is your response to an influenza vaccine may differ when it's the first time you've ever been exposed to influenza or the vaccine. You may have a better response. Some people think that the first influenza you're ever exposed to, through the vaccine or nature, has a long-term effect on your immune response.

But we were very pleased to see the better response in children this year.

Mr. HARPER. So how do we communicate that? Why is it especially important for school-age children to get vaccinated? How do we communicate that? And, certainly, you would agree that's true?

Dr. SCHUCHAT. Yes, we have simplified our recommendations for children, and now we recommend everybody 6 months and over get a flu vaccine every year. The first time you're getting a flu vaccine, if you're a young child, you're supposed to get two doses of the vaccine.

Communication about vaccination has to be multisectoral. We think the healthcare provider, pediatricians, are the most important influence on kids getting vaccinated, but we also use trusted channels, social media, and other influencers.

Mr. HARPER. We've obviously seen that the number of children receiving the flu vaccine has remained steady at just under 60 percent, and the number of adults receiving flu vaccines remains fairly steady, between 41 and 43 percent.

So how do we do that, not just for children but for adults also, to communicate to America the importance of being vaccinated with a flu vaccine?

Dr. SCHUCHAT. Yes, there is a nuanced message, because being open and honest is really important and not promising that the vaccine will, you know, cure cancer—although we have a vaccine that does that, actually, the HPV vaccine. Sorry. But I think Americans want us to be open and honest about vaccine information.

We know that flu vaccines can prevent disease and reduce severity, and we know that they can also prevent spread. Children are very important in getting flu disease but also in spreading it. And so getting higher coverage among children is in the whole public's interest.

Mr. HARPER. That's great. Thank you very much.

The Chair now recognizes Ranking Member DeGette for the purposes of questions.

Ms. DEGETTE. Thank you, Mr. Chairman.

Dr. Fauci, I think everybody on this panel agrees with you when you said that we need to get away from the antiquated production model, which the egg is.

And I know the chairman, particularly, appreciated your slideshow. He's new to this subcommittee, so he hasn't seen it be-

fore. And he told me he was a chemistry major, so I'm happy to have him to educate me.

So the recombinant-based vaccine was only 3 percent last year, from what I understand. I'm wondering if you can talk to me, what the barriers are for moving from the current methods that we have, the egg-based methods which are used for the majority, to this cutting-edge vaccine.

And I'm going to ask everybody else for their opinion, too, on that.

Dr. FAUCI. Yes. I think there are a few barriers, at least two, that stand out. One is that there are still scientific challenges to get the very best recombinant DNA technology. And there are three or four or five in addition to the one that was used in the 3 percent from protein sciences, the flu block. There are things that are even better than that.

So we need—and that was part of what I put, Congresswoman DeGette, in the strategic plan, that there are scientific gaps in the arena of what we call platform technology, is different types of vaccine. That's the first one, scientific obstacle.

The second one that's important is that, whenever you have, as Dr. Gottlieb mentioned, whenever you have something that's time-honored and works and is safe, there is an understanding—fundamental underlying inertia for companies to make a change to something in which they were going to have to make a major investment in resources to switch over from one to the other. Because you have one that you know that works—

Ms. DEGETTE. Sort of.

Dr. FAUCI [continuing]. One that you know is safe. They're going to have to make an investment.

But the thing that I think we need to emphasize is that we've got to go there. We can't stay stuck in the old technologies.

Ms. DEGETTE. Thank you.

Dr. BRIGHT, do you want to add to that?

Dr. BRIGHT. I think everything Dr. Fauci said is spot-on, I mean, but, in addition to those, it's about the capacity and the yields of the new technology. So we've had 70 years to optimize the efficiency and the yields for an egg-based vaccine. We've had about 5 years to try to work on optimization of recombinant and cell-based vaccines. So it's remarkable to see the progress that's being made in those companies to improve the efficiency of production and the yields of those vaccines.

Another challenge, however, though, the vaccine is blended together in the marketplace, so there hasn't been a focus on getting the differentiated data set to show the benefit and effectiveness of egg-based or non-egg-based vaccines. We all know the benefits of non-egg-based vaccines is speed and flexibility. Those are critical for a pandemic response. That's critical if we had to change late season for a virus drift. We're also getting the additional data now to understand the true effectiveness difference.

Ms. DEGETTE. So, Dr. Gottlieb, did you want to add anything?

Dr. GOTTLIEB. I agree with my colleagues.

I'll just add, you know, with the recombinant processes, one of the challenges still is the cell culture and the yield you're able to derive using the recombinant process. And, you know, while we've

commented that we observed better efficacy with the cell-based vaccine this year relative to the egg-based vaccine, it is the case that in some years we observe better efficacy with the egg-based process versus a cell-based process.

And so I think the underlying message here, from my standpoint, is the egg-based process is safe and effective; it works. The challenge with it—

Ms. DEGETTE. Sort of.

Dr. GOTTLIEB [continuing]. Is it's hard to scale—

Ms. DEGETTE. Right.

Dr. GOTTLIEB [continuing]. And it's hard to make a midseason change.

Ms. DEGETTE. And it's also hard if you have a pandemic flu that hits.

I'm wondering if any of you can—Dr. Schuchat, did you want to add? I didn't want to leave you out.

Dr. SCHUCHAT. Yes, just to say that the investments in vaccine effectiveness studies on a large scale are really worthwhile. It's only recently that we could tell you that the effectiveness against H3N2 is less than against H1N1 and B or that children have higher—

Ms. DEGETTE. Because the studies were—and so, aside from funding, I'll ask any of you—I don't have much time left—is there anything else Congress can do to move this along? Because I remember years ago asking the same questions. I'm glad we've made some progress, but clearly we're going to have to get to the gold standard.

Dr. GOTTLIEB. I mean, if I may just quickly comment, Congresswoman, as part of the President's budget this year, we did put forward a proposal to try to make investments in continuous manufacturing. That was geared towards this kind of an opportunity—

Ms. DEGETTE. Yes.

Dr. GOTTLIEB [continuing]. To try to establish the regulatory parameters to enable these innovations to come forward.

Ms. DEGETTE. Yes.

Anyone else?

Dr. BRIGHT. And, again, I mean, it does go back to funding in some ways, but just to support, to encourage the movement to the modernized technologies, in addition to expanding their domestic capacities that we have and when we need them.

Ms. DEGETTE. OK. I think you can say we have got bipartisan support for that on this committee.

Right, Mr. Chairman?

Mr. HARPER. I believe that's true.

Ms. DEGETTE. Yes.

Mr. HARPER. That's great.

Ms. DEGETTE. Thank you. I yield back.

Mr. HARPER. The gentlewoman yields back.

The Chair will now recognize the chairman of the Energy and Commerce Committee, Greg Walden, for the purposes of questions.

Mr. WALDEN. Thank you, Mr. Chairman.

And, again, thanks to our very distinguished panel of witnesses not only for your help in crafting public policy here today but also



the great work you do every day to improve the lives and the health of Americans and, frankly, people around the world.

Dr. Gottlieb, one of the treatments that's available for individuals who get the flu is the antivirals. We've talked some about that today. Are antiviral drugs more effective the earlier they are given?

Dr. GOTTLIEB. They are, Congressman.

Mr. WALDEN. And how do they work?

Dr. GOTTLIEB. The currently available—

Mr. WALDEN. To a layperson.

Dr. GOTTLIEB [continuing]. Antiviral drug works by blocking a different step in the replication cycle of the virus itself than the one that the vaccine targets. The vaccine targets the ability of the virus to attach to the cell membrane in the lungs.

Mr. WALDEN. All right.

And, last week, the FDA issued a press release warning of fraudulent and unapproved flu products. Why did you feel that press release was necessary, to warn consumers to be cautious?

Dr. GOTTLIEB. Because we see a lot of efforts online to try to entice consumers to purchase products that we know are fraudulent, that are making false claims, false and misleading claims, that are claiming to have antiviral and anti-flu effects, when, in fact, they are not approved for those purposes, including dietary supplements.

Mr. WALDEN. And if consumers feel like they've been defrauded, what should they do?

Dr. GOTTLIEB. Well, they should certainly—I think any consumer that feels they might have used a product that was making an inappropriate or fraudulent claim should certainly contact their medical provider and certainly refer the information to FDA.

Mr. WALDEN. All right.

And, recently, as I mentioned in my comments at the beginning, a new antiviral drug was approved in Japan, or is in that process, that supposedly has the potential to treat the flu in just one dose.

Are you familiar with that product? And can you talk to us a little bit about whether that's the case and what we might see here?

Dr. GOTTLIEB. So I'm familiar with the product. I would defer to my colleagues on the panel a little bit.

I will just say that what the sponsor has said publicly is that they plan to submit an application at some point this year. And they currently have disclosed that they have some studies ongoing in the U.S. looking at a high-risk population.

This is a drug that acts at a different point in the replication cycle, mechanistically an earlier stage in replication than the other drug that you referenced, so it is differentiated. And the other, you know, potential opportunity is that the onset of action appears to be earlier than the currently available antiviral.

I think the bottom-line message is that we are very interested in having a spectrum of antiviral drugs that act differently, at different points in the virus. In case the virus itself becomes resistant to one approach at targeting the virus, we have backups and we have alternative approaches.

Mr. WALDEN. Very good.

Other members of the panel want to comment on that specifically? And then I have one other question.

Dr. BRIGHT. If I can add to that, yes, so BARDA has been engaged with this company developing this drug for quite some time, as well as some other companies that we're supporting to develop new classes of antiviral drugs for influenza.

It's critical to note that we have not had a new class of antivirals approved for influenza in over 20 years.

Mr. WALDEN. Wow.

Dr. BRIGHT. We rely on a single class of influenza antivirals now. And the virus, as we know, continues to change, and resistance to that class of antivirals continues to emerge. And it's very concerning in avian influenza viruses, such as pandemic strains H5N1, H7N9, to see these high levels of resistance emerging to that class of drugs.

So it's remarkable that this company took the lead in developing a new class of antiviral drug. It has attributes of a single dose. Instead of 5 days at twice-a-day dosing, it brings down the viral load in the patient very rapidly, faster than the currently approved antiviral drugs. And it has this new mechanism of action, so if a virus becomes resistant to the only approved class of drugs we have now, this drug would still work. And it could also be used potentially in combination with the existing class of drugs.

Another thing exciting about this drug is that they've partnered now with a U.S.-based company. That U.S.-based company has taken the lead in bringing that to the FDA for discussions and consideration for approval in the United States. And their plans are to transfer the knowledge and the capability to manufacture that drug in the United States in the near term.

So, again, it's one of about a dozen or a half-dozen promising candidates with new mechanisms of action, several of those supported by BARDA, and even monoclonal antibodies, to make better treatments for flu.

Mr. WALDEN. Yes, Dr. Fauci?

Dr. FAUCI. So I can't help myself on this, Mr. Chairman, for the benefit of Chairman Harper, is that Rick Bright said that this is very extraordinary, that the company did this. However, the first recognition of this particular mechanism was in a paper from 1979 in the Proceedings of the National Academy of Sciences—

Mr. WALDEN. Who authored that?

Dr. FAUCI [continuing]. By the National Institutes of Health. OK? It's entitled, "Transfer of 5'-terminal cap of globin mRNA to influenza viral complementary RNA during transcription."

So it just goes to show you, I mean, that basic science is the root of everything we do, even something that 20 years later turns into a product made by a Japanese company.

Thank you.

Mr. WALDEN. We'll let you—that's good. You know? And that's part of why we did 21st Century Cures, to continue that funding and that cycle and all.

I was hoping to ask a question about domestic manufacturing of vaccines and threats and opportunities, but my time has expired, and maybe we can get some of that as the hearing continues.

Thank you again for your good work and for being here.

Mr. HARPER. The gentleman yields back.

The Chair will now recognize the gentlewoman from Illinois, Ms. Schakowsky, for 5 minutes.

Ms. SCHAKOWSKY. I want to thank you, Dr. Fauci, for that addendum and the information. I think it's really important to appreciate how much our researchers and the Federal Government contribute to addressing these.

So I have some basic questions as just an ordinary consumer and person. I think, Dr. Schuchat, you might be the person to ask. Can you tell us generally how easy it is to spread the flu virus person to person?

Dr. SCHUCHAT. Yes. It varies by strains, but, of course, this is one of the more infectious or contagious viruses that we have. And so, in a household, spread is frequent. In a school, spread is frequent.

It can be spread through respiratory droplets or through fomites, sort of, on your hand. That's why you've seen us so many times say cover your nose when you cough or sneeze and don't touch your eyes or mouth after you're—you know, with your hands—you know, sort of, wash your hands frequently.

Ms. SCHAKOWSKY. And how long is a person contagious with the flu? Is it possible for a person to be contagious and not know it?

Dr. SCHUCHAT. You can be contagious before you develop symptoms, and usually we say about 24 or 48 hours after the fever goes down. Again, with influenza, it varies by virus and by year. But that's sort of the general facts.

Ms. SCHAKOWSKY. Twenty-four hours to 48 hours after the fever.

Dr. SCHUCHAT. After the fever goes down.

Ms. SCHAKOWSKY. Goes down. Right.

So the CDC recommends that people stay home for 24 hours after their fever breaks. But I wanted to point out, according to the Bureau of Labor Statistics, 28 percent of workers have no access at all to paid sick leave. And this is particularly a problem for those in the lowest-wage jobs. One-third of lower-paid workers, including those who work in fields such as food preparation, have no paid sick leave. And, in fact, the United States is the only industrialized country in the world without paid sick leave.

I leave this to anyone, really. Can you explain why it's important for people to stay home when they're sick?

Dr. SCHUCHAT. We're really trying to limit the spread of the virus. And so staying home while you're sick will help you heal but also keep you from the spreading to others.

Ms. SCHAKOWSKY. So, in 2016, the National Bureau of Economic Research found that if paid sick leave were mandated it would prevent 100 flu-like infections per week for every 100,000 people. So, when people can stay home when they're sick, people are less likely to get the flu.

So I know this is not your jurisdiction, but I think it's just important to note that some of the cautions that we suggest for people are really hard to abide by if you are depending on that paycheck for that day. I think we need to think about it. It's a public health issue. Paid sick leave is a public health issue.

I wanted to also note that Heather Holland in Texas, a Texas mother, 38 years old, died because she could not afford the co-pay

for Tamiflu, which was \$116. And she had insurance, so this was a co-pay.

So, first of all, Tamiflu, would it have helped her if she took it in time? And what do we say about that? \$116 for a low-income family is a lot of money even when insured.

Can someone comment on that?

Dr. SCHUCHAT. Yes, I can just say that, in response to the spot shortage of antiviral medicines this year, we worked closely with manufacturers and pharmacies and insurers, and we learned that there was actually plenty of supply, but much of what was available was brand product rather than the generics, the newer generics.

We did, in the midst of the season, get some agreement by pharmacies or the pharmacy benefit managers and insurers to offer the brand as either generic or preferred brand, which would give a lower co-pay.

But, of course, you know, that's a very, very sad story. We don't know that antivirals will cure a person. The best data suggest they shorten the course of illness. And, of course, being able to start them quickly is what we think helps reduce the severe complications.

Ms. SCHAKOWSKY. So, then, in conclusion, let me just say, paid sick leave and affordable pharmaceuticals, very important issues that we need to grapple with as we put in context this flu virus.

Thank you.

Mr. HARPER. The gentlewoman yields back.

The Chair will now recognize the gentleman from Virginia, Mr. Griffith, for 5 minutes.

Mr. GRIFFITH. Thank you very much, Mr. Chairman. It's been very informative. I appreciate all the testimony. You all are doing some great things.

I will tell you that it's kind of interesting and it was timely, on February 28, just a week or so ago, I got an email from a constituent who apparently keeps up with a lot of these issues. And he started talking in his email about NanoFlu and what was going on and how we might be able to push that particular product forward.

And one of the things that he raised in his comments that I thought was very interesting, he says that they are planning—they have already done phase 1, so I guess we are coming to you, Dr. Gottlieb. But he said they have already done phase 1 human trials, they don't plan to do phase 2 until the third quarter of 2018 because, obviously, you want the flu to be out there to a certain extent in order to be able to test it.

And he said, you know, I don't—and I'm going to quote from his email: I do not understand why the FDA and CDC do not push a vaccine like this ahead. It would seem to me they might push for phase 2 in Australia this year and possibly a phase 3 this year in the U.S. That could make the vaccine available for flu season starting in the fall of 2019.

If the Government is really serious about speeding up the slow approval process and reducing health costs, a process like this would help to do it. And I ask the question because it makes some sense. Why are we using the Australian flu season to start testing

some of these new ideas? You've indicated—several of you have—that there may be 20 or 30 or 40 new products out there, and wouldn't we be able to shorten that time period, particularly in the live trials, if we did some of it here and some of it there where they have the opposite seasons and a different flu season as well?

So I'll start with you and welcome anybody's comments.

Dr. GOTTLIEB. I'll just kind of briefly, Congressman, I'm not sure I'm familiar with the product. I think this is a recombinant vaccine that you're referring to.

Mr. GRIFFITH. I believe that it is, too. I'm not well enough versed in it to say, but yes—and it's been tested mostly, comparing it to the vaccine for senior adults. But since I'm apparently rapidly approaching that category, very interested. I turn 60 later this month.

Dr. GOTTLIEB. I will just say, it is not uncommon to see products tested in the southern hemisphere, so I'm not sure what the particular circumstance here is, but that is a common phenomenon with new products. You'll see them tested there to help accelerate the development process.

Mr. GRIFFITH. So I can tell Paster Jones that you all are not against it?

Dr. GOTTLIEB. You could pass on to anyone that we are willing to actively engage with any sponsor that is developing an innovative product in this space.

Dr. FAUCI. Mr. Griffith, it's not a testing in Australia versus here. The product that your constituency was referring to is the nanoparticle that has gone into phase 1, the one I showed you the model of.

Mr. GRIFFITH. Right.

Dr. FAUCI. The reason it's not going to go into phase 2 from the standpoint of until the end of the year is really a production capability, it's what Dr. Gottlieb referred to when he said what we haven't gotten efficient yet is the yield of this.

So we don't have enough GMP product to start a phase 2 until the end of 2018. It's not that we—that the FDA is holding us up or anything, it's just that we don't have enough product.

Mr. GRIFFITH. Well, I really appreciate that. Dr. Bright, did you want to weigh in?

Dr. BRIGHT. I was going to weigh in and say that it's very typical. When you develop any new vaccine, it's difficult and takes time. When you develop an influenza vaccine, you have to time it with an outbreak of influenza. So as long as it's under a USIND, we are very flexible in allowing the companies to get the data and conduct clinical studies wherever flu might be in the world, as long as it's following that IND process.

Mr. GRIFFITH. Well, that's great. And I appreciate you all helping me answer that question. And I know that Mr. Jones, who I spoke with yesterday, makes sure I could say his name in public, he'll be very pleased to hear that as well.

Let me ask this, because the chairman brought it up just—and if you all can get to it briefly, the domestic supply and the threat of maybe having our supply mostly offshore of our flu vaccines. And it doesn't matter to me who wants to respond to that. I guess that would be ASPR, is that correct?

Dr. BRIGHT. We work very hard—it's a very important question. We worked very hard over the last years and invested great sums of money to make sure that we can develop these vaccine and get them licensed. It is critical now that we expand that domestic manufacturing capacity, so not only they are able to meet a seasonal market demand, but they are also available when we need them for a pandemic. And in a pandemic situation we know we cannot import vaccines from other countries easily. So the domestic manufacturing capability for these modern technologies for recombinant cell-based is absolutely critical to our national security.

Mr. GRIFFITH. And I appreciate that and my time is just about up. But I would say, could you please let us know what we can do to assist in trying to get more onshore production?

And I yield back.

Mr. HARPER. The gentleman yields back. The Chair now recognizes the gentlewoman from Florida, Ms. Castor, for 5 minutes.

Ms. CASTOR. Thank you, Mr. Chairman, and thank you to all the witnesses for being here and everything you do to help keep Americans healthy and safe. We're now exiting peak flu season, but we're entering allergy season. And what I've learned over the past decade is that our allergy seasons are longer and more intense, we have hotter days. Back home in Florida the pollen is already raging.

What advice do you give to families with children and others in vulnerable populations that are on alert because of the intensity of the flu season as they begin to deal with allergies? When is the appropriate time to head right to the doctor's office and get checked out if you have a flu? Is it the onset of fever? Dr. Fauci?

Dr. FAUCI. If the question you're asking is the overlap between the two, how do you know which one it is, well, the recommendations that we get from the CDC, and I'll yield to Dr. Schuchat in a second, but what we say is that if you have symptoms that persist, number one, that's certainly something you want to go to a physician for.

If you have a situation where you look like you're recovering and then you have a relapse, it could possibly be a bacterial infection. But, importantly, if you fall into one of the risk categories—elderly, underlying disease like heart disease, chronic lung disease, diabetes, obesity, pregnancy, child from birth to 4 years old—you should not hesitate to see a physician because that's the group that really would benefit from getting an antiviral drug like Tamiflu.

And that's the reason why the CDC recommends that we do that, and, Ann, you might want to—

Dr. SCHUCHAT. Yes, and I would just say that even though we're pleased that the peak of the season seems to have passed, there's still a lot of flu out there. And the B strains are more common right now than they were a few weeks ago. So we certainly look for fever with flu or flu-like illness.

But as Dr. Fauci did describe, the warning signs, things like getting better and then getting worse is a warning sign, difficulty breathing, a very high persistent fever. For children, you know, not being very responsive or being hard to wake up. Those are really important things to—

Ms. CASTOR. You know, and I continued to hear the refrain from folks that don't get a flu shot that they don't get it because last

time they got it, it made them sick, and that's the reason that they don't get the flu shot.

What do you say to them?

Dr. SCHUCHAT. You know, the influenza vaccines don't cause flu. There can be some feeling of not feeling that well, but in general we give flu vaccines during a season where there is a lot of other stuff out there, and so the symptoms are rarely related to the vaccine itself.

Dr. FAUCI. We had a season this year, because before we had the peak of flu, there was a lot of parainfluenza and even respiratory syncytial virus among adults that we were seeing, at least at our clinical center at the NIH. So that was before the onset of the flu. And people were saying, well, I already got the flu, therefore I don't need the vaccine. Well, they are wrong on two accounts. One, because they likely did not have the flu, they had something else. And even if you have the flu, you should still get a vaccine because there are other components in the vaccine that could protect you against the other flu that is circulating besides just H3N2.

Dr. BRIGHT. And if I might add. This is an area for innovation that is just screaming out to give patients more information, more knowledge about what they might be exposed to in the home. And that's one of the reasons that we're trying to drive diagnostics out of centralized laboratories into the homes of the patients so they have actionable information to be able to distinguish that they have a bacterial infection or a viral infection or flu or some other area. So they can take responsible action to get treated sooner and to take actions to reduce the spread of that virus.

Ms. CASTOR. Thank you. And preliminary estimates are that this year's flu vaccine shows 36 percent effectiveness. I want to hear more about how we assess vaccine effectiveness to better understand this measure.

Dr. Schuchat, how do we test for vaccine effectiveness, and what does it mean that the vaccine is 36 percent effective? And is it true that this effectiveness was different for different age groups?

Dr. SCHUCHAT. Yes. We have a multistate, multisite network that tests vaccine effectiveness, and they evaluate people who come in with symptoms consistent with influenza, do laboratory testing of them. Those who have confirmed laboratory-proven influenza are enrolled as cases, and those who have those symptoms but didn't have laboratory-confirmed influenza are enrolled as controls. We compare vaccination history verified with the records in them, and then do sort of math to calculate what the vaccine effectiveness is against particular types and particular age groups.

The larger the sample, the more we can look at ages and narrow categories and look at the different types. We do interim estimates in January and February each year, and then end-of-season estimates. If we had a larger sample, a larger network, we would be able to more reliably look at the age groups, but potentially also look at different types of vaccine like the cell-based or the egg-based.

Ms. CASTOR. And I guess your overriding message is, no matter what percentage you come up with, it benefits you, and your neighbors, and your family to get your flu shot?

Dr. SCHUCHAT. The flu vaccine is the best way to protect yourself and your family against influenza. And some protection is better than no protection.

Ms. CASTOR. Thank you very much.

Mr. HARPER. The gentlewoman yields back. The Chair now recognizes the gentleman from Texas, Dr. Burgess, for 5 minutes.

Mr. BURGESS. Thank you, Mr. Chairman. While we're on the commercial to get your flu shot, I want to thank Dr. Fauci personally because he told me in December I better get it, and I did, and I didn't get the flu this year. So I thank you for that. And it has been a tough year back in Texas.

Dr. Bright, you said that there had not been a new antiviral introduced in the past 20 years. Did I understand that correctly?

Dr. BRIGHT. That is true. Well, 1999 with the approval of oseltamivir and zanamivir.

Mr. BURGESS. So let me—I guess this question is for Dr. Fauci and Dr. Gottlieb, Dr. Fauci as far as the scientific side, Dr. Gottlieb as far as the regulatory side. Why is this so difficult? A virus is a pretty simple organism, nowhere near as sophisticated as a mammalian cell. It seems like selective toxicity, you talk about it a little bit in that—in that paper that you showed us. It seems like that should be pretty straightforward.

Dr. FAUCI. It seems that way, but—and you're right, there are targets in the replication cycle, polymerase and other—pronase and other inhibitors that we have for that. The interesting thing is that we—even though we're doing the fundamental basic research to examine that, we have not had an overwhelming amount of interest on the part of companies, which is the reason why BARDA has been so important in helping to chaperone the companies along to get involved in this.

So it really is, you're right, it isn't a completely insurmountable scientific problem. It has a replication cycle. Remember, when we pull all of that effort into looking at the various aspects of the replication cycle of HIV, we came up with now a total of 30 effective drugs. There's no reason why, with the right scientific and industry interest in it, that we couldn't do the same thing. And I just yield to my colleagues to my left to amplify that.

Mr. BURGESS. Well, Dr. Gottlieb, then I assume that on the regulatory side that is something—that is work you'd be prepared to take up?

Dr. GOTTLIEB. Well, absolutely. And I think there's a lot of interest in seeing differentiated products put forward that can address the flu for a whole host of reasons, not least of which is the strategic rationale of having that available. I will just comment that, you know, the standards for approval are relatively straightforward, and I think the agency would show a lot of interest and a lot of high level attention to products that were put forward to try to address both pandemic flu as well as the seasonal flu.

I will comment, that there have been safety issues associated with products that have been in early stages of development in the past. But one of the bigger challenges, quite frankly, and this is a little bit outside of my remit, but they have been commercial challenges. Just the ability to get a commercial return on a property to target the seasonal flu.



And I will remind the committee that at the time that the agency approved Tamiflu, the agency was roundly criticized by many outside groups, not by Congress, but by outside groups, for that approval, who commented that a drug that diminished flu symptoms by 1.42 days wasn't something the agency ought to be approving.

And so our mindset has changed around this, but in some quarters not entirely.

Mr. BURGESS. That's an incredibly important point. I was in practice at that time, and that did temper your judgment about writing this prescription, regardless of cost. If it's really only marginally effective, why put someone through the potential side-effects that possibly would occur.

Dr. BRIGHT, you provide the market that Dr. Fauci referenced is not readily available, so it's hard to incent companies to take these challenges on. But you provide the market, right? You're going to be the one—the bulk purchaser of this stuff?

Dr. BRIGHT. Well, the marketplace for antivirals for seasonal flu is the marketplace. And I don't think there's full appreciation and recognition of the impact and benefit that one could receive from getting an antiviral drug in a timely manner when they are infected with influenza.

We had a new antiviral, same class from the Tamiflu, approved by a company, BioCryst, called Peramivir, just a few years ago, and there's still very little up-take of that new antiviral drug. And it is a single-dose, IV-administered drug. So there is hesitancy in the marketplace to develop new antiviral drugs, even with benefits and reducing viral load and saving the—reducing the severity of illness, if the marketplace and the patients and the healthcare system doesn't understand and appreciate the power of that drug.

Mr. BURGESS. Let me just ask you a related question. You talked about bringing down the viral load. Kind of encountered when Ebola was causing all of the problems, the rapid reduction of the viral load caused kind of a Herxheimer reaction in some patients, and that caused some concern. Is that—is that something, a phenomenon with which you are concerned with these types of medications?

Dr. BRIGHT. We haven't seen that with the influenza antiviral drugs. Reduction of viral load, we believe would lead to less transmission. We believe it would lead to less severe illness in influenza antivirals.

Mr. BURGESS. Yes, Dr. Fauci.

Dr. FAUCI. And in Ebola, that was more a viremia, as opposed to what you see with influenza, which is mostly a local reaction in the lung. So you would you not expect a Herxheimers with that.

Mr. BURGESS. Very good. Thank you, Mr. Chairman. I yield back.

Mr. HARPER. The gentleman yields back. The Chair will now recognize the gentleman from New York, Mr. Tonko, for 5 minutes.

Mr. TONKO. Thank you, Mr. Chairman. And welcome to our panelists. Data from the National Immunization Survey found that fewer than half of children and adults were vaccinated by November of this current flu season. Only about 40 percent of people 6 months and older received the flu vaccine. These numbers appear to be just about what they were in the last couple of flu seasons. I'm just interested in hearing from this panel about why you be-

lieve these numbers continue to be in that realm, and just how do you approach that as an organization?

Dr. Schuchat, the data show that nearly 60 percent of Americans did not take advantage of that flu vaccination, is that an accurate number?

Dr. SCHUCHAT. You know, the numbers that you're citing are from November, and those are our early results. By the end of the season, what we've seen in the last several years, is that about 48 percent of Americans get the flu vaccine, it's much higher in children, about 59 percent, and 43 or so in adults. There's a lot of mixed messages. And when we—the thing with influenza, when we have a year like this where it's so severe, everybody actually knows how bad it can be, but then there's also questions about whether the vaccine is helpful or not.

It's really important for the clinicians and for us in public health to remind people that the vaccine has provided protection, particularly in children, and that getting the vaccine each year is worthwhile.

Mr. TONKO. And, Dr. Schuchat, again, and Dr. Gottlieb, perhaps, what have your organizations been doing to improve the rate, if anything?

Dr. SCHUCHAT. Right. We do quite a bit of research on communication. We've done, I think, more than 30 studies to test messages over the past 18 years to try to understand what motivates individuals, as well as what influences clinicians in giving a strong recommendation. One of the biggest factors for patients is a strong recommendation from their doctor.

We've seen an increase in OB/GYNs recommending the vaccine and more women who were pregnant getting the flu vaccine each year, really after they saw how severe it was in 2009 when you were pregnant and got influenza. But we've probably hit a wall right now. And after this season, there's a lot of concern that—we don't know how the medical community or public is going to react, so we're out there doing research right now and testing messages for next fall.

We do use multiple channels in doing communication about vaccine, both traditional channels and social media, trying to find influencers and address the myths that people have.

Mr. TONKO. Uh-huh. And Dr. Gottlieb.

Dr. GOTTLIEB. I would just comment, I think the CDC has the most robust platform for communicating, but we not only echo the CDC recommends and their statements, but put out a number of our own to try to build on that. I think one of the things we did this season in particular was try to be very transparent about what we were learning about the vaccine effectiveness as we learned it. To continue to remind providers, in particular, and consumers, that this vaccine still had efficacy, and it had efficacy in particular against H1N1 and the B virus, which tend to peak later in the season.

So even if people perceived it as being less efficacious against H3N2, there was still a lot of value in getting vaccinated because later in the season you tend to see an upswing in the H1N1 and B virus, as we're seeing right now. And the vaccine was actually quite effective against those strains.

Mr. TONKO. And in terms of the 100 percent number that, obviously, is something that sounds like you shoot for, how important is it to reach that?

Dr. SCHUCHAT. With many vaccines, there's direct protection, but also indirect protection and, at a certain level, the higher proportion of the population that's vaccinated, they may actually be helping others not get sick. So, in particular, I think the pediatric vaccination is important for the children, it's also important for the adults that often get flu from their kids or from their grandkids.

Mr. TONKO. Representative Castor touched on this a bit. This season we saw many new reports focused on the fact that the vaccine was only 36 percent effective. In addition, some inaccurate and misleading social media posts have warned people against vaccinating themselves or their children.

Dr. Schuchat, does CDC have any way of tracking how these media sources impact the number of people who are actually vaccinated?

Dr. SCHUCHAT. We do assess attitudes periodically and try to understand whether there are rumors that are resonating or not. You know, when we do research on "why didn't you get vaccinated for influenza?" we hear more often about the—well, "I heard that's not an effective vaccine" rather than concerns about safety or concerns about cost. But I think that it varies for each vaccine what the barriers are or what the concerns are.

We work hard through our messaging, but also through partners and others to get the word out. You know, sometimes the faith-based community can reach a lot of people in some areas. There are mommy bloggers that are influential in some circles. Friends and family can be influential. Our most critical audience are clinicians and healthcare providers because doctors, nurses, pharmacists have a lot of influence on people's behavior.

Mr. TONKO. Thank you very much. Anyone else that wants to comment on that? If not, I yield back and thank you, Mr. Chairman.

Mr. HARPER. The gentleman yields back. The Chair now recognizes the gentlewoman from Indiana, Mrs. Brooks, for 5 minutes.

Mrs. BROOKS. Thank you, Mr. Chairman. And thank you to all the panelists for being here, and thank you for your service. As the panel here may or may not know, Congresswoman Eshoo and I recently started a biodefense caucus. I would encourage all of the Members here to consider joining our caucus. And this is in a lead-up to the hopeful reauthorization of PAHPA. But I want to go back a little bit because during the 21st Century Cures debate, we did get signed into law the return of contracting of authority to BARDA.

And I'm curious, Dr. Bright, this was something—we wanted it restored, it was in the original passage when BARDA was created, but it's my understanding there's been some hesitation by the contracting office to move the contracting back over to BARDA. Has that contracting authority yet been properly restored use since it was authorized and passed into law under 21st Century Cures?

Dr. BRIGHT. Thank you for the question, and we are so grateful for 21st Century Cures to include that in the law that passed. It's critically important. It has not been finalized yet, but it's important

to know that it is part of an overall realignment of the entire ASPR organization, and we look forward to the full implementation of that very soon.

Mrs. BROOKS. And what is the holdup?

Dr. BRIGHT. The holdup is the alignment with the overall realignment of ASPR. So it's fully intended that Dr. Kadlec, our ASPR and I, are in full alignment to implement this as quickly as possible. We anticipate it will be done in a matter of months.

Mrs. BROOKS. OK. We'll continue to ask questions until we hear that what was authorized in the 21st Century Cures has been implemented.

I do have a question, though, in the original PAHPA, it's my understanding that BARDA was also given other transaction authority to reduce regulatory burden on the Federal contracting process that could both inhibit innovation and our preparedness. Is BARDA able to use that other authority that was in the original—in the original PAHPA bill?

Dr. BRIGHT. BARDA has been using other transactional authorities. Now, we have six of those in place with different industry entities. The process of getting the other transactional authorities is still—a process is going to outside senior procurement executive that we're working on improving the effectiveness and efficiency of that process now with our ASPR, but we are finding ways to utilize that OTA, other transactional authority, effectively.

Mrs. BROOKS. OK. Thank you. Sorry, you're on the hot seat today, however, with the reauthorization of PAHPA coming—due to expire in September, talk to me about the administration's fiscal year 2019 request of \$250 million for pandemic influenza.

Can you explain, at BARDA, authorization of pan flu program, BARDA, I assume is beneficial, assuming it is authorized or reauthorized, would you agree?

Dr. BRIGHT. It's absolutely essential, yes.

Mrs. BROOKS. Can you share with us how those funds would be used to prepare for the next influenza pandemic?

Dr. BRIGHT. I described for you a lot of the work that has been done already with the investment that we've been provided and supplemental funds, and those funds are all obligated. And we've made great strides with our industry partners to make our country better prepared for pandemic influenza, but there is a lot of work still to be done.

As I said, we need to expand the access and availability of the vaccines we created so they are useful and available for all ages. We still need to develop additional antiviral drugs. We need more drugs, more treatment options to treat people who are severely ill and hospitalized with influenza. And we need to do a better job with our diagnostics as well. We need to make sure the diagnostics are in the hands of the people who need them so they can get treated sooner and they can take responsible actions to reduce the spread of that virus. All of that work is yet to be done.

In the context of still sustaining what we've built, we have to sustain the infrastructure, that is our response capability for pandemic in our Nation. So in the context of sustaining and filling the gaps, that's how we would support and use those funds.

Mrs. BROOKS. And in my 47 seconds left, can you talk about the importance of sustained and robust funding? Sustained being the critical word here, and why is that so critically important?

Dr. BRIGHT. The sustainment of the funding, because we rely on these facilities of these companies to be available and producing a vaccine that is warm based, so when we need it, we need it quickly, that they have the staff in place and the capabilities in place, and that the FDA is able to continue reviewing and approving that facility.

It's important that we don't let our eye off the ball for sustainment. If the factories close, we have no response, we gain nothing. At the same time we must sustain our momentum in conducting and supporting the phase 2 and phase 3 clinical studies for additional recombinant-based technologies for vaccines, for the platform-based technologies in the regional manufacturing process across our country so we can rely on those quickly when he would need them for a pandemic.

Mrs. BROOKS. Thank you. I yield back.

Mr. HARPER. The gentlewoman yields back. The Chair will now recognize the gentlewoman from California, Mrs. Walters, for 5 minutes.

Mrs. WALTERS. Thank you, Mr. Chairman. California was hit particularly hard this year by the flu season. In my home of Orange County, especially suffered with well over twice the number of flu cases compared to last year. Orange County had at least a dozen influenza-related deaths in individuals under the age of 65. Yet, we all know that seniors are particularly susceptible to the flu. The CDC states that at least 75 percent of flu-related deaths occur in people 65 and older.

My district is home to a large retirement population so I am especially concerned about the health of this group during flu season. While the overall flu vaccine effectiveness rate for this year is 36 percent, the effectiveness rate can vary depending on age group. For instance, last year the overall effectiveness rate was 40 percent, and the effectiveness rate for seniors was only 25 percent.

One would suspect the vaccine effectiveness rate is lower for vulnerable populations like seniors, but I notice that the 2016–2017 vaccine effectiveness rate was much more effective for children, another vulnerable population. Some of my colleagues have asked what accounts for the variability in flu vaccine effectiveness among age groups, what can be done to improve vaccine effectiveness for seniors?

Dr. SCHUCHAT. I can begin. There have been efforts to develop different influenza vaccine products, particularly for seniors and others with weaker immune systems. One such approach is a high-dose product that has been licensed. Another approach is adjuvanted. A key strategy that we have at CDC is to make sure that patients and clinicians know that people at high risk for complications, including seniors, get promptly treated with antivirals if they do get sick. But the immune system does age, and we think that the frailer, elderly have a poor response to many vaccines, including flu.

Dr. FAUCI. Whenever we have a situation, for example, when we are making a vaccine for a possible pandemic, we always test it not

only in healthy adults, but we also test it in the elderly to make sure that the dose and the regimen that we have gives a comparable response that a younger person would have. So that's part of the testing. And as Dr. Schuchat said, the two major areas or the higher dose, which is recommended for seniors, it's a much higher dose than the dose that you give to a healthy young person, as well as using adjuvants, which is a product that is not a vaccine but boosts the response to the vaccine.

Dr. BRIGHT. If I could add, too. This is a lesson from pandemic influenza vaccine development that we can transition to seasonal influenza vaccine development. We know in a pandemic vaccine we have to have higher doses of antigen and we have to have adjuvants in those vaccines that makes them immunogenic and effective across all age groups.

I recently in the last two weeks visited the senior leadership of each of the licensed influenza vaccine manufacturers for the United States, and talked to them about this challenge about what their thoughts and strategies and how we can improve the effectiveness of our existing vaccines while we wait for the universal flu vaccine. Each of them is poised and strategic in thinking about ways to add the adjuvant and increase the dose of their vaccine. They are all partnered and interested in utilizing cell-based and recombinant-based vaccines as well to try to improve the effectiveness over the egg-based vaccines.

Dr. GOTTLIEB. I'll just comment very briefly, Congresswoman. We're actively looking at data as to the relative effectiveness of the vaccine with the MF59 adjuvant and the high dose vaccine in elderly patients relative to the normal vaccine, the regular-dose vaccine with the 15 micrograms of antigen.

I think if we do observe differences between the high-dose vaccine—the efficacy of the high dose vaccine or the vaccine with the adjuvant in it relative to the regular seasonal flu vaccine. It could offer some clues as to why the vaccine overall was less effective against H3N2. We will have that data available, hopefully, shortly. We're working very closely with CMS to drive those results and we are going to make it available as soon as we have it.

Mrs. WALTERS. OK. And, Dr. Schuchat, in 2009, the FDA approved a high-dose version of the flu vaccine for elderly individuals. There is a study that indicates the high-dose vaccine was 24.2 percent more effective in preventing the flu in adults aged 65 and older, as compared to the standard-dose vaccine.

Can you elaborate on whether the high-dose vaccine would significantly reduce flu-related deaths among seniors?

Dr. SCHUCHAT. Even a 20-some percent superior response is still not, you know, 100 hundred percent, because of the weaker immune response that seniors get. We have the market of the higher-dose product has been increasing since it became available. CDC doesn't recommend a preference for the high-dose over the regular-dose vaccine. One of the things we found is that the vaccine that they have at the doctors' office or the pharmacy is the one that you should get because there may not be the other product if you're looking for it.

But I think the additional studies that FDA is doing with CMS, and we've done with CMS in the past, have helped us build this evidence base of what's the best way to protect seniors.

Mrs. WALTERS. Thank you, and I'm out of time. Thank you.

Mr. HARPER. The gentlewoman yields back. The Chair will now recognize the gentleman from Texas, Mr. Green, for 5 minutes.

Mr. GREEN. Thank you, Mr. Chairman. Thank you and the ranking member for allowing me to wave on. I am an alumni of this subcommittee. And thank you for allowing me to be here. I want to thank the Chair for holding this hearing on the current flu season.

The 2017–2018 flu season has been one of the worst in recent years, resulting in tens of thousands of hospitalizations, and likely thousands of flu-related deaths around the country. There has been some advances in both vaccine technology and in antiviral drugs, which hopefully can both reduce the number of people who get the flu and help those who do get it to recover more quickly.

I understand there's a new vaccine production method based on recombinant protein technology that makes it less likely for a vaccine to mutate, as it is being grown. Dr. Bright, BARDA has supported development of several vaccines based on this technology, as well as the development of cell-based vaccines and antigen sparing vaccines. Can you explain why BARDA has chosen to support research on these vaccine production methods rather than the egg-based production methods?

Dr. BRIGHT. Thank you for that question. We primarily focus on supporting those new modern technologies to be able to respond faster and more effectively to a pandemic response. We know that we can cut out steps necessary to make a vaccine in the egg. You don't need a virus to grow—to produce vaccines in the recombinant system. You can start from a gene sequence and rapidly go into production of your vaccine. This affords us great flexibility and great speed compared to egg-based vaccines.

We're learning now that investments in those new technologies might also offer advantages of a potentially more effective flu vaccine. What's critical to know about this, too, is it's one thing to license those vaccines and make them available, but if they're not available in sufficient supply and don't have the capacity to produce it, then they are not penetrating the marketplace, and those companies are frail and are vulnerable, at risk of going out of business after huge investment, if that vaccine is not used.

Mr. GREEN. Thank you. Commissioner Gottlieb, preliminary data suggests that some of the newer vaccines such as high-dose vaccines may offer greater protection. Is there enough data on these vaccines for the FDA to recommend these vaccines over others? If not, what type of data would the FDA need to make such a recommendation?

Dr. GOTTLIEB. Congressman, we're still evaluating, at least from this season, some of the data relative to the high-dose vaccine and the vaccine with the adjuvant to see its relative effectiveness against H3N2. And when we start to speculate around different theories around why the vaccine overall—and vaccines historically might be—have been less efficacious against H3N2. One of the theories that you would put on the table, certainly, is perhaps you

might require a higher dose of antigen in order to have an adequate immune response against H3N2.

So it's something that we're going to need to consider among many other possibilities on why historically we haven't seen a robust immune response from the—against H3N2 from vaccines generally, when we look back around past seasons. The one thing we did observe so far this season was that the vaccine produced in cells, the cell-based vaccines, we had about 20 million doses produced in cells this year. Those do appear to be—to have provided more protection on a relative basis of around 20 percent than the egg-based vaccines. And, again, we aren't sure of the reasons why, but it does lead to some hypotheses around why maybe generally speaking we haven't seen as much—as robust response against H3N2 historically as we'd like.

Mr. GREEN. I know there are a number of new antivirals in the pipeline, including some that may treat the virus at the beginning of the life cycle. Dr. Bright, can you explain why these drugs differ from those currently on the market, and how they might help us treat the flu in a new way?

Dr. BRIGHT. Absolutely. I think that's important to recognize. The one class of drug that we have that's effective on the market today is called a neuraminidase inhibitor. It binds to an active pocket of a surface protein of the virus and it really blocks the virus after it's already replicated from breaking away from an infected cell and going on to infect other cells.

These new antiviral drugs are working on the replication cycle of the virus before it reproduces itself and buds away. Because they work in a different part of the virus life cycle, they also can be effective if the virus mutates and becomes resistant to the single class of drug that we have available in the market today. So it's critical that we have these different approaches to antiviral drugs.

Mr. GREEN. Thank you. Mr. Chairman, I know I'm out of time and your courtesies, I have some other questions that I'd like to submit if it's allowed.

And thank our panel for being here today. We're looking for that light at the end of the tunnel, and I just appreciate each of you all partnering with each other to deal with it. Obviously, the flu is terrible, but you know there are a lot of other bugs out there that we'd like to deal with, too. Thank you, Mr. Chairman.

Mr. HARPER. The gentleman yields back. And I will remind Members that they do have 10 business days to submit questions for the record, and I ask the witnesses to agree to respond promptly should you get additional questions in writing.

I want to thank you for your time being here today. It's very informative. And, Dr. Fauci, I enjoyed the slide presentation, I felt like I should get some college credit for that—to see that.

Dr. FAUCI. You got it.

Mr. HARPER. But to visualize that and to see how it's better to attack the stem instead of the head, and actually give you a good visual was very informative. And, you know, one day we'll be in here and we'll be discussing that effective universal flu vaccine that we know we all desire to see. And I was going to say, I hope we continue to take steps, even if they are nanoparticle steps, to



get to that conclusion. But, again, thanks each of you for being here. The subcommittee hearing is adjourned.

[Whereupon, at 12:35 p.m., the subcommittee was adjourned.]

[Material submitted for inclusion in the record follows:]

PREPARED STATEMENT OF HON. FRANK PALLONE, JR.

Mr. Chairman, since 2010, influenza has caused millions of illnesses, hundreds of thousands of hospitalizations, and perhaps as many as 56,000 deaths throughout the country. This is a very serious issue that should concern all of us who play a role in advancing public health.

Right now, we are in the middle of a particularly bad flu season. According to the CDC, more than 23,000 people have been hospitalized this season, mostly due to the H3N2 strain of flu. Tragically, more than 100 children have already died this year.

Seasonal flu is particularly challenging for our public health agencies to address. Flu viruses tend to mutate and change constantly, and we do not yet have the ability to predict in advance how severe a flu season will be, when it will peak, or what flu strains will dominate. There are also many things that we still do not know about why the flu vaccine is more effective for certain people, and how someone's health status may affect the body's immune response.

I am encouraged by the recent initiative announced by NIH which intends to study these very issues, with the goal of producing a universal flu vaccine that is effective against a broader range of flu strains. I know that the Biomedical Advanced Research and Development Authority (BARDA) is supporting vital research in this area, as well.

This is all critically important. And while we wait for the results of this research, we know that there is one thing we can all do to help stop the spread of the flu—we can all get vaccinated.

Thanks to the Affordable Care Act, flu and other immunizations are required to be covered by health insurance without any copayments or coinsurance. It is free, and it is as easy as going to the pharmacy around the corner. So there is no good reason for Americans not to get a flu shot.

Annual flu vaccination continues to be the best method for preventing flu and its potentially severe complications in both children and adults. Getting the flu vaccine reduces flu-associated illness and adverse health outcomes.

This is true even in a year where the flu vaccine is less effective. For example, during the 2014–15 flu season, the vaccine was only 20 percent effective at preventing infection. Nonetheless, that vaccine formulation still prevented an estimated 1.6 million illnesses, nearly 50,000 influenza-associated hospitalizations and an estimated 1,500 deaths.

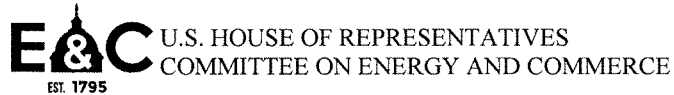
Moreover, flu shots do not only protect the vaccinated. Vaccinating yourself not only increases the odds that you won't get sick this season, but also protects everyone you come in contact with, such as your older parents, or your sister's new baby.

Unfortunately, up to 60 percent of Americans were not vaccinated against the flu this year. I look forward to hearing from CDC about what strategies have improved vaccination rates in the past, and how we can continue to increase the rates going forward.

Additionally, the fact that the vaccine was only 36 percent effective this year highlights the need to improve our vaccine manufacturing process, as well as our ability to treat patients if they do become infected.

I look forward to hearing from today's witnesses about new technologies and initiatives to enhance the effectiveness of vaccines and of antiviral medications.

I want to thank all the witnesses for coming today. The work your agencies are doing is a key part of our Nation's flu preparedness efforts. I look forward to hearing from each of you about what your agencies are doing to improve flu vaccine effectiveness, vaccination rates, and influenza treatment methods.



March 6, 2018

TO: Members, Subcommittee on Oversight and Investigations

FROM: Committee Majority Staff

RE: Hearing entitled "Examining the U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza."

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## **I. Introduction**

The Subcommittee on Oversight and Investigations will hold a hearing on Thursday, March 8, 2018, at 10:00 a.m. in 2123 Rayburn House Office Building. The hearing is entitled "Examining U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza." The Subcommittee will examine the U.S. Department of Health and Human Services' efforts to combat seasonal influenza, develop an effective influenza vaccine, and to prepare a long-term strategy to improve seasonal influenza preparedness.

## **II. Witnesses**

- Anne Schuchat, M.D. (RADM, USPHS), Acting Director, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services;
- Anthony S. Fauci, M.D., Director, National Institute of Allergy and Infectious Diseases, National Institutes of Health, U.S. Department of Health and Human Services;
- Rick A. Bright, Ph.D., Deputy Assistant Secretary for Preparedness and Response, Director of the Biomedical Advances Research and Development Authority, Office of the Assistant Secretary for Preparedness and Response, U.S. Department of Health and Human Services; and
- Scott Gottlieb, M.D., Commissioner of Food and Drugs, U.S. Food and Drug Administration, U.S. Department of Health and Human Services.

## **III. Background**

### **A. Overview of Seasonal Influenza in the United States**

Influenza (the "flu") is a contagious respiratory illness caused by different virus strains and can range in severity from mild to deadly. In both its seasonal and pandemic forms, influenza is an ongoing public health concern and is a leading cause of death in the United

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States.<sup>1</sup> The number of illnesses, hospitalizations, and deaths per year can vary depending on several factors, including but not limited to, the severity of the flu season, characteristics of the prevalent viruses, and the effectiveness of the vaccine. The Centers for Disease Control and Prevention (CDC) estimates that, on an annual basis since 2010, influenza has resulted in between 9.2 million and 60.8 million illnesses, 140,000 and 710,000 hospitalizations, and 12,000 and 56,000 deaths.<sup>2</sup> As noted in CDC's 2018 Congressional Budget Justification, a 2007 study estimated that more than \$10 billion is spent each year in direct medical costs for hospitalizations and outpatient visits from seasonal influenza-related complications.<sup>3</sup>

Although CDC estimates the number of flu-associated deaths, CDC does not calculate the exact number of individuals that die each year from the seasonal flu.<sup>4</sup> The agency cannot calculate this number for a variety of reasons, including but not limited to the fact that: (1) states are not required to report individual seasonal flu cases or deaths of people aged 18 years and older to CDC; (2) many influenza-related deaths, such as from pneumonia, may not include any mention of influenza on the death certificate; (3) it can be difficult to identify which cases to include in an analysis since many patients (especially the elderly) may die from pneumonia unrelated to influenza; and (4) most people who die from seasonal flu-related complications are not tested for flu or they seek medical care when flu can no longer be detected. Given the difficulties in calculating the precise number of flu-related deaths, researchers use a variety of modeling techniques to estimate deaths. CDC looks at two categories of underlying cause of death information listed on death certificates to estimate the number of flu-associated deaths: (1) pneumonia and influenza (P&I) causes; and (2) respiratory and circulatory (R&C) causes.<sup>5</sup>

<sup>1</sup> Seasonal flu is an outbreak that follows predictable seasonal patterns. Pandemic flu is a worldwide outbreak of a new form of flu virus, which can spread easily from person to person because most people have little to no immunity. Centers for Disease Control and Prevention, *How is Pandemic Flu Different from Seasonal Flu?* (last updated Dec. 9, 2016), <https://www.cdc.gov/flu/pandemic-resources/basics/about.html>.

<sup>2</sup> Based on 2015 data, CDC estimated that the number of deaths in 2015 caused by influenza and pneumonia was 57,062. U.S. Dep't of Health and Human Services, Centers for Disease Control and Prevention, National Center for Health Statistics, *Health, United States, 2016, With Chartbook on Long-term Trends in Health* (2016), <https://www.cdc.gov/nchs/data/health/us16.pdf#019>; Centers for Disease Control and Prevention, *Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States* (last updated Apr. 19, 2017), <https://www.cdc.gov/flu/about/disease/2015-16.htm>; Centers for Disease Control and Prevention, *Estimating Seasonal Influenza-Associated Deaths in the United States—Questions and Answers* (last updated Jan. 29, 2018), [https://www.cdc.gov/flu/about/disease/us\\_flu-related\\_deaths.htm](https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm); Centers for Disease Control and Prevention, *Deaths and Mortality* (last updated May 3, 2017), <https://www.cdc.gov/nchs/fastats/deaths.htm>; Centers for Disease Control and Prevention, *Seasonal Influenza-Associated Hospitalizations in the United States* (last updated at Dec. 9, 2016), <https://www.cdc.gov/flu/about/qa/hospital.htm>.

<sup>3</sup> Centers for Disease Control and Prevention, *FY 2018 Congressional Justification*, at 46 (2018), <https://www.cdc.gov/budget/documents/fy2018/fy-2018-cdc-congressional-justification.pdf>; See also Molinari, et al., *The annual impact of seasonal influenza in the US: measuring disease burden and costs*, VACCINE Volume 25 Issue 27 (Jun. 28, 2007).

<sup>4</sup> Centers for Disease Control and Prevention, *Estimating Seasonal Influenza-Associated Deaths in the United States—Questions and Answers* (last updated Jan. 29, 2018), [https://www.cdc.gov/flu/about/disease/us\\_flu-related\\_deaths.htm](https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm).

<sup>5</sup> *Id.*

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While the flu may result in death or hospitalization, most individuals that get the flu only have a mild illness and will recover in less than two weeks.<sup>6</sup> Examples of flu-related complications include bronchitis, pneumonia, ear infections, sinus infections, and worsening of chronic health conditions. Those individuals that are at high risk for developing flu-related complications include, but are not limited to, children younger than 5 years of age, adults 65 years of age and older, pregnant women, residents of long-term care facilities, American Indians and Alaska Natives, and individuals with certain medical conditions.<sup>7</sup> Although individuals aged 65 and older are more likely to receive the flu vaccine than younger adults, hospitalization rates for the flu are likely to be highest among the elderly. For example, for the 2014-2015 flu season, 38 percent of people aged 18-64 years old received the vaccination while 66.7 percent of people aged 65 years and older received the vaccination.<sup>8</sup> About 75 percent of the estimated hospitalizations for the 2014-2015 flu season, however, occurred in individuals aged 65 years and older.<sup>9</sup>

Overall, seasonal influenza has significant health and economic impacts, with a cumulative impact as serious as a pandemic. According to the World Health Organization (WHO), annual seasonal influenza epidemics result in about 3 million to 5 million cases of severe illness and about 250,000 to 500,000 deaths worldwide, which is likely an underestimation. As noted in a 2012 report by the Center for Infectious Disease Research and Policy, “[t]hese figures indicate that the cumulative health impact of seasonal influenza over the last century rivals the potentially explosive, but time-limited, impact of the four pandemics of the past 100 years.”<sup>10</sup>

## B. Types of Influenza and Influenza Detection

The influenza virus is made up of single-stranded ribonucleic acid (RNA) segments that are coated by a nucleoprotein.<sup>11</sup> The four types of influenza viruses (A, B, C, and D) are primarily distinguished by their different main nucleoproteins.<sup>12</sup> Influenza types A, B, and C have the capacity to infect humans whereas influenza type D primarily infects cattle and is not

<sup>6</sup> Centers for Disease Control and Prevention, *People at High Risk of Developing Flu-Related Complications* (last updated Jan. 23, 2018), [https://www.cdc.gov/flu/about/disease/high\\_risk.htm](https://www.cdc.gov/flu/about/disease/high_risk.htm).

<sup>7</sup> *Id.*

<sup>8</sup> Centers for Disease Control and Prevention, *Flu Vaccination Coverage, United States, 2014-15 Influenza Season* (last updated Jun. 23, 2016), <https://www.cdc.gov/flu/fluview/coverage-1415estimates.htm#age-group-adults>.

<sup>9</sup> Centers for Disease Control and Prevention, *Estimated Influenza Illnesses and Hospitalizations Averted by Vaccination – United States, 2014-15 Influenza Season* (last updated Feb. 17, 2017), <https://www.cdc.gov/flu/about/disease/2014-15.htm>.

<sup>10</sup> Center for Infectious Disease Research and Policy, University of Minnesota, *The Compelling Need for Game-Changing Influenza Vaccines: An Analysis of the Influenza Vaccine Enterprise and Recommendations for the Future*, at 11 (October 2012).

<sup>11</sup> University of Pittsburgh Schools of the Health Sciences, *50-year-old flu virus model revamped, revealing pandemic prediction possibilities*, SCIENCE DAILY (Jul. 13, 2017), <https://www.sciencedaily.com/releases/2017/07/170713154853.htm>; Nara Lee, et al., *Genome-wide analysis of influenza viral RNA and nucleoprotein association*, NUCLEIC ACIDS RESEARCH Volume 45, Issue 15 (Sept. 6, 2017).

<sup>12</sup> Centers for Disease Control and Prevention, *Types of Influenza Viruses* (last updated Sept. 27, 2017), <https://www.cdc.gov/flu/about/viruses/types.htm>.

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known to infect or cause illness in humans.<sup>13</sup> Influenza types A and B are the two main types of viruses that cause seasonal epidemics and typically pose the most serious public health threat. Influenza type C infections are not believed to cause epidemics and instead typically cause mild respiratory illness.<sup>14</sup>

The CDC adheres to an internationally accepted naming convention for influenza viruses that was accepted by the World Health Organization (WHO) in 1979.<sup>15</sup> Each influenza virus is named according to: (1) the antigenic type (e.g., A, B, C); (2) the host of origin for viruses that did not originate in humans (e.g., swine, chicken, etc. (no host of origin designation is provided for human-origin viruses)); (3) geographical origin (e.g., Denver, Taiwan, etc.); (4) strain number (e.g., 15, 7, etc.); (5) year of isolation (e.g., 2009, etc.); and (6) the hemagglutinin (H) and neuraminidase (N) antigen in parentheses for influenza type A viruses (e.g., (H1N1) (influenza types B and C do not receive these subtype classifications)).<sup>16</sup>

Recently, influenza strains have grown increasingly complex and have been distributed more broadly across the globe. In February 2015, the WHO noted that the world needed to be concerned about the diversity and geographical distribution of influenza viruses:

The current global influenza situation is characterized by a number of trends that must be closely monitored. These include: an increase in the variety of animal influenza viruses co-circulating and exchanging genetic material, giving rise to novel strains... The diversity and geographical distribution of influenza viruses currently circulating in wild and domestic birds are unprecedented since the advent of modern tools for virus detection and characterization. The world needs to be concerned.<sup>17</sup>

The news of this array of genetic forms of influenza is partly a result of improved surveillance measures.<sup>18</sup> Many scientists, however, believe that the pace of evolution in influenza is speeding up because of human movement and trade along the Asian flyway, giving more opportunities for various types of flu to come together, mix their RNA genetic material, and form novel strains.<sup>19</sup> This in turn is making it harder for scientists to predict which forms of influenza are likely to hit human populations during certain seasons, accurately predict what type of vaccine is likely to be effective for that season, and anticipate the movement of flu viruses from wild birds to domestic fowl, fowl to humans, humans to swine, and swine back to humans.

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<sup>13</sup> *Id.*

<sup>14</sup> *Id.*

<sup>15</sup> *Id.*

<sup>16</sup> *Id.*

<sup>17</sup> World Health Organization, *Warning signals from the volatile world of influenza viruses* (Feb. 2015), <http://www.who.int/influenza/publications/warningsignals201502/en/>.

<sup>18</sup> Lauren S. Polansky, et al., Centers for Disease Control and Prevention, *Improved Global Capacity for Influenza Surveillance*, EMERGING INFECTIOUS DISEASES Volume 22, Number 6 (June 2016).

<sup>19</sup> Laurie Garrett, *The Year of the Flu*, COUNCIL ON FOREIGN RELATIONS (Feb. 4, 2015), <https://www.cfr.org/expert-brief/year-flu>.

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The consequences from the emergence of so many novel viruses “for animal and human health are unpredictable yet potentially ominous.”<sup>20</sup>

Moreover, the influenza viruses constantly change through antigenic drift and antigenic shift.<sup>21</sup> Antigenic drift refers to small changes in the genes of influenza viruses that happen continually over time as the virus replicates.<sup>22</sup> Antigenic shift occurs when there is an abrupt, significant change in the influenza A virus resulting in a new H and/or new H and N proteins. Because the H and N antigens can undergo antigenic shifts or drifts and mutate frequently, influenza type A typically causes the most severe outbreaks. Indeed, new influenza type A viruses are constantly emerging from animal reservoirs, and there has been a tenfold increase in the number of human infections with different novel influenza A viruses since the 1990s.<sup>23</sup> One specific subtype of influenza type A, H3N2, has a faster mutation rate than H1N1 or influenza B viruses, and this fast mutation rate can make it even more difficult to make an effective vaccine during some flu seasons.<sup>24</sup> For example, during the 2014-2015 flu season, the prevalent strain of H3N2 was different than the strain used during the season’s vaccine development.<sup>25</sup>

Because of the potential for changes in the circulating influenza viruses, close monitoring of influenza viruses is required to evaluate the potential impact of the seasonal flu on public health. CDC uses different tests to characterize influenza viruses, including genomic sequencing and Hemagglutinin Inhibition Assay (HAI/HI assay).<sup>26</sup> For samples collected and submitted to U.S. laboratories from October 1, 2017 to February 17, 2018, CDC has antigenically or genetically characterized 1,599 influenza viruses, including 350 influenza A(H1N1)pdm09 viruses, 779 influenza A(H3N2) viruses, and 470 influenza B viruses.<sup>27</sup> For H3N2, the analysis for the 2017-2018 flu season “revealed extensive generic diversity with multiple clades/subclades co-circulating.”<sup>28</sup>

<sup>20</sup> World Health Organization, *supra* note 17.

<sup>21</sup> Centers for Disease Control and Prevention, *How the Flu Virus Can Change: “Drift” and “Shift,”* (last updated Sept. 27, 2017), <https://www.cdc.gov/flu/about/viruses/change.htm>.

<sup>22</sup> *Id.*

<sup>23</sup> National Academies of Sciences, Engineering, Medicine, *Rapid Medical Countermeasure Response to Infectious Diseases, Workshop Summary*, at 48 (Oct. 12, 2015), <https://www.nap.edu/read/21809/chapter/6?term=1990#48>.

<sup>24</sup> Helen Branswell, ‘The problem child of seasonal flu’: Beware this winter’s virus, STAT NEWS (Jan. 8, 2018), <https://www.statnews.com/2018/01/08/flu-virus-h3n2/>.

<sup>25</sup> Laurie Garrett, *The Year of the Flu*, COUNCIL ON FOREIGN RELATIONS (Feb. 4, 2015), <https://www.cfr.org/expert-brief/year-flu>; Hearing before the U.S. House of Representatives, Committee on Energy and Commerce, “U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?” (Nov. 19, 2015).

<sup>26</sup> *Id.*

<sup>27</sup> *Id.* Some researchers have found that the H3N2 virus poses significant health risks and results in more fatalities and hospitalizations than other influenza viruses. Dan Gray, *2018 Flu Season Off to a Strong, Potentially Dangerous Start*, HEALTHLINE (Jan. 3, 2018), <https://www.healthline.com/health-news/2018-flu-season-potentially-dangerous-start#1>.

<sup>28</sup> Laurie Garrett, *supra* note 25.

### C. Seasonal Flu Vaccine: Development and Effectiveness

#### i. Seasonal Influenza Vaccine Development

The flu vaccine must be reformulated on an annual basis to protect against strains expected to be most prevalent that year since circulating influenza virus strains constantly change.<sup>29</sup> Each year, public health experts, including those from the Food and Drug Administration (FDA), WHO, and CDC, study influenza virus samples and global disease patterns to identify virus strains likely to cause the most illness during the upcoming season.<sup>30</sup> In collaboration with other partners, WHO recommends the specific vaccine viruses that should be included in the next season's influenza vaccines in the northern hemisphere every February (WHO made recommendations for the 2018-2019 flu season on February 22, 2018).<sup>31</sup> The FDA then selects the strains for inclusion in the annual influenza virus that is sold and distributed in the United States based on that information and the recommendations of FDA's Vaccines and Related Biological Products Advisory Committee (VRBAC).<sup>32</sup>

Most flu vaccines are injectable and include inactivated influenza vaccines and recombinant influenza vaccines.<sup>33</sup> Typically, the influenza vaccine protects against three or four different flu viruses.<sup>34</sup> There are three different production technologies approved by the FDA for injectable influenza vaccines: (1) egg-based flu vaccine; (2) cell-based flu vaccine; and (3) recombinant flu vaccine.<sup>35</sup> The egg-based manufacturing process, which has been used for more than seventy years and takes about 22 to 24 weeks to produce, is the most common way that flu vaccines are manufactured in the U.S. The cell-based production process, approved by FDA in 2012, takes about 16 to 17 weeks to manufacture the vaccine. The recombinant flu vaccine manufacturing process, approved by FDA in 2013, can produce flu vaccines in the shortest amount of time at about 12 to 15 weeks.

<sup>29</sup> Centers for Disease Control and Prevention, *Selecting Viruses for the Seasonal Influenza Vaccine* (last updated May 4, 2016), <https://www.cdc.gov/flu/about/season/vaccine-selection.htm>.

<sup>30</sup> In the northern hemisphere, seasonal influenza may begin as early as August and generally diminishes by April. Typically, influenza activity peaks between December and February in the United States but may peak later in the season. Centers for Disease Control and Prevention, *Estimated Influenza Illnesses, Medical Visits, Hospitalizations, and Deaths Averted by Vaccination in the United States* (last updated Apr. 19, 2017), <https://www.cdc.gov/flu/about/disease/2015-16.htm>.

<sup>31</sup> Centers for Disease Control and Prevention, *Selecting Viruses for the Seasonal Influenza Vaccine*, *supra* note 29.

<sup>32</sup> Robert Lowes, *First Quadrivalent Flu Vaccine Approved, Debuts Fall 2013*, MEDSCAPE (Mar. 1, 2012), <https://www.medscape.com/viewarticle/759517>.

<sup>33</sup> Immunization Action Coalition, *Influenza Vaccine Products for the 2017-2018 Influenza Season* (last visited Mar. 2, 2018) <http://www.immunize.org/catg.d/p4072.pdf>.

<sup>34</sup> The trivalent influenza vaccine protects against three different influenza viruses (including an influenza A(H1N1) virus, an influenza A(H3N2) virus and one influenza B virus) and the quadrivalent influenza vaccine protects against four influenza viruses (including an influenza A(H1N1) virus, an influenza A(H3N2) virus and two influenza B viruses). Centers for Disease Control and Prevention, *Quadrivalent Influenza Vaccine* (last updated Dec. 14, 2017), <https://www.cdc.gov/flu/protect/vaccine/quadrivalent.htm>.

<sup>35</sup> Centers for Disease Control and Prevention, *How Influenza (Flu) Vaccines are Made* (last updated Nov. 7, 2016), <https://www.cdc.gov/flu/protect/vaccine/how-fluvaccine-made.htm>.

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In 2003, FDA approved a nasal spray flu vaccine—called FluMist—that includes a live attenuated influenza vaccine for certain ages.<sup>36</sup> Because data from observational studies showed low effectiveness of FluMist Quadrivalent against a specific strain of the influenza virus in the United States during the 2013-2014 and 2015-2016 flu seasons, however, CDC's Advisory Committee on Immunization Practices (ACIP) did not recommend that the live attenuated vaccine be used by individuals for the past few years.<sup>37</sup> In February 2018, ACIP recommended that the live attenuated influenza vaccine be included on the 2018-2019 influenza vaccination schedule for individuals for whom it is appropriate.<sup>38</sup>

For the 2017-2018 flu season, manufacturers estimated that they would provide about 151 million to 166 million doses of injectable vaccine in the United States, and as of February 9, 2018, about 154.7 million doses of the seasonal influenza vaccine had been distributed.<sup>39</sup> About 119 million doses of the influenza vaccine were expected to be quadrivalent flu vaccine.<sup>40</sup> According to the CDC, about 15 to 20 percent of the supply of flu vaccine for the 2017-2018 flu season was manufactured through non-egg based manufacturing and about 80 to 85 percent was manufactured through the egg-based manufacturing process.<sup>41</sup>

## ii. Seasonal Influenza Prevention and Vaccine Effectiveness

The primary method for preventing influenza is annual vaccination. According to the CDC's 2018 Congressional Budget Justification, vaccination prevented approximately 5.1 million influenza illnesses, 2.5 million influenza-associated medical visits, and 71,000 influenza-associated hospitalizations during the 2015-2016 influenza season.<sup>42</sup> Similarly, a 2015 study published in the journal *Vaccine* showed that the seasonal flu vaccine prevented more than 40,000 flu-associated deaths in the United States from 2005-2006 through 2013-2014.<sup>43</sup>

<sup>36</sup> U.S. Food and Drug Administration, *FDA Information Regarding FluMist Quadrivalent Vaccine* (last updated Jan. 26, 2018), <https://www.fda.gov/BiologicsBloodVaccines/Vaccines/ApprovedProducts/ucm508761.htm>.

<sup>37</sup> Centers for Disease Control and Prevention, *Prevention and Control of Seasonal Influenza with Vaccines, Recommendations of the Advisory Committee on Immunization Practices—United States, 2016-17 Influenza Season* (Aug. 26, 2016), [https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm#T1\\_down](https://www.cdc.gov/mmwr/volumes/65/rr/rr6505a1.htm#T1_down).

<sup>38</sup> Molly Walker, *ACIP Reinstates FluMist for 2018-2019 Flu Season*, MEDSCAPE (Feb. 21, 2018), <https://www.medpagetoday.com/meetingcoverage/acip/71298>.

<sup>39</sup> Centers for Disease Control and Prevention, *Seasonal Influenza Vaccine Supply & Distribution* (last updated Feb. 15, 2018), <https://www.cdc.gov/flu/about/qa/index.htm>. For the 2017-2018 season, 13 influenza vaccine products were approved by 6 different manufacturers. Out of these 13 influenza vaccine products, 9 were egg-based trivalent/quadrivalent inactivated influenza vaccine (injectable), 2 were trivalent/quadrivalent recombinant hemagglutinin influenza vaccine (injectable), 1 was a cell culture-based vaccine quadrivalent inactivated influenza vaccine, and 1 was live attenuated influenza vaccine (CDC's Advisory Committee on Immunization Practices did not recommend use of this vaccine for the 2017-18 flu season). One of the nine egg-based trivalent/quadrivalent inactivated influenza vaccines (injectable) was an adjuvanted trivalent inactivated influenza vaccine. Immunization Action Coalition, *supra* note 33.

<sup>40</sup> Centers for Disease Control and Prevention, *Quadrivalent Influenza Vaccine* (last updated Dec. 14, 2017), <https://www.cdc.gov/flu/protect/vaccine/quadrivalent.htm>.

<sup>41</sup> U.S. House of Representatives, Comm. on Energy and Commerce, Subcomm. on Oversight and Investigations, 115th Cong., Committee Staff Phone Briefing with the U.S. Dep't of Health and Human Services (Mar. 1, 2018).

<sup>42</sup> Centers for Disease Control and Prevention, *FY 2018 Congressional Budget Justification*, *supra* note 3, at 47.

<sup>43</sup> Ivo Foppa, et al., *Deaths averted by influenza vaccination in the U.S. during the seasons 2005/06 through 2013/14*, *VACCINE* Volume 33 (June 12, 2015), [www.sciencedirect.com/science/article/pii/S0264410X15002315](http://www.sciencedirect.com/science/article/pii/S0264410X15002315).



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Likewise, according to a 2017 study published by the CDC in the journal *Pediatrics*, the influenza vaccine reduced the risk of flu-associated death by half for children with underlying high-risk medical conditions and by nearly two-thirds for healthy children.<sup>44</sup>

Indeed, research indicates that even if the flu vaccine fails to protect an individual against being infected with the flu, the vaccine may help reduce severe outcomes.<sup>45</sup> According to CDC estimates, approximately 80 percent of flu-associated deaths in children in past flu seasons have occurred in children who were not vaccinated.<sup>46</sup> Likewise, a 2017 study by the CDC showed that receiving the flu vaccine reduced severe outcomes in hospitalized patients by reducing deaths, reducing intensive care unit (ICU) admissions, reducing ICU length of stay, and reducing overall duration of hospitalization among hospital patients.<sup>47</sup> The study found that vaccinated adults were 52 to 70 percent less likely to die than unvaccinated flu-hospitalized patients and experienced additional benefits.<sup>48</sup>

CDC estimates the effectiveness of the flu vaccine every year, and by effectiveness, CDC means the rate at which the vaccine prevents a person from getting sick with the flu and going to the doctor (the effectiveness rate does not, however, account for other potential benefits from receiving the flu vaccine such as helping reduce severe outcomes if an individual gets the flu).<sup>49</sup> Recent studies show that seasonal flu vaccination typically has an effectiveness rate in the range of 40 to 60 percent.<sup>50</sup> According to CDC, the overall, adjusted vaccine effectiveness estimates for influenza seasons from 2005 to 2018 ranged from 10 to 60 percent.<sup>51</sup>

***CDC's Adjusted Vaccine  
Effectiveness Estimates<sup>52</sup>***

Year	Adjusted Overall Vaccine Effectiveness
2004-2005	10%
2005-2006	21%
2006-2007	52%
2007-2008	37%
2008-2009	41%

<sup>44</sup> Centers for Disease Control and Prevention, *CDC Study Finds Flu Vaccine Saves Children's Lives* (Apr. 3, 2017), <https://www.cdc.gov/media/releases/2017/p0403-flu-vaccine.html>.

<sup>45</sup> *Id.*

<sup>46</sup> Centers for Disease Control and Prevention, *Estimating Seasonal Influenza-Associated Deaths in the United States—Questions and Answers* (last updated Jan. 29, 2018), [https://www.cdc.gov/flu/about/disease/us\\_flu-related\\_deaths.htm](https://www.cdc.gov/flu/about/disease/us_flu-related_deaths.htm).

<sup>47</sup> Centers for Disease Control and Prevention, *New CDC Study Shows Flu Vaccine Reduces Severe Outcomes in Hospitalized Patients* (May 25, 2017).

<sup>48</sup> *Id.*

<sup>49</sup> Centers for Disease Control and Prevention, *Frequently Asked Flu Questions 2017-2018 Influenza Season* (last updated Mar. 1, 2018), <https://www.cdc.gov/flu/about/season/flu-season-2017-2018.htm>.

<sup>50</sup> Centers for Disease Control and Prevention, *Vaccine Effectiveness—How Well Does the Flu Vaccine Work?* (last updated Oct. 3, 2017), <https://www.cdc.gov/flu/about/qa/vaccineeffect.htm>.

<sup>51</sup> Centers for Disease Control and Prevention, *Seasonal Influenza Vaccine Effectiveness, 2005-2018* (last updated Feb. 15, 2018), <https://www.cdc.gov/flu/professionals/vaccination/effectiveness-studies.htm>.

<sup>52</sup> *Id.*

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2009-2010	56%
2010-2011	60%
2011-2012	47%
2012-2013	49%
2013-2014	52%
2014-2015	19%
2015-2016	48%
2016-2017	40%
2017-2018	36%

Vaccine effectiveness can differ depending on the age of the individual that received the vaccination. For example, for the 2016-2017 flu season, the vaccine was 61 percent effective for individuals aged 6 months to 8 years, 19 percent effective for individuals aged 18 to 49 years, and 25 percent effective for people aged 65 years and older.<sup>53</sup> Similarly, preliminary data shows that the vaccine effectiveness for all virus types for the 2017-2018 flu season differed by age group—statistically significant protection was found among children aged 6 months through 8 years (a vaccine effectiveness rate of 59 percent was found) and adults aged 18 to 49 years old (a vaccine effectiveness rate of 33 percent was found).<sup>54</sup> CDC’s analysis of the preliminary data did not find any statistically significant protection in other age groups.<sup>55</sup>

Moreover, vaccine effectiveness also differs across different subtypes of influenza. Research shows that the flu vaccine typically is more effective against influenza B and influenza A(H1N1) viruses than influenza A(H3N2) viruses.<sup>56</sup> Some researchers have raised concerns about the decline in effectiveness of the annual influenza vaccine, especially for the H3N2 virus.<sup>57</sup> A 2016 meta-analysis of 56 past studies published in PubMed and Embase found that, on average, the seasonal flu vaccine was 33 percent effective against the H3N2 virus, 54 percent effective against influenza B, 61 percent effective against the H1N1pdm09 virus, and 67 percent effective against H1N1.<sup>58</sup> During the 2017-2018 flu season in the United States, preliminary data shows that while the flu vaccine had an overall vaccine effectiveness rate of 36 percent, vaccine effectiveness for all ages was 25 percent against type A(H3N2) viruses, 67 percent against influenza A(H1N1)pdm09 viruses, and 42 percent effective against influenza B virus infection.<sup>59</sup>

<sup>53</sup> Robert Lowes, *Flu Vaccine Efficacy Slips from Prior Estimate, CDC Says*, MEDSCAPE (June 23, 2017), <https://www.medscape.com/viewarticle/882075>.

<sup>54</sup> Centers for Disease Control and Prevention, *Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness – United States, February 2018* (Feb. 16, 2018), <https://www.cdc.gov/mmwr/volumes/67/wr/mm6706a2.htm#contribAff>.

<sup>55</sup> *Id.*

<sup>56</sup> Centers for Disease Control and Prevention, *Vaccine Effectiveness—How Well Does the Flu Vaccine Work?* (last updated Oct. 3, 2017), <https://www.cdc.gov/flu/about/qa/vaccineeffect.htm>.

<sup>57</sup> Nicholas C. Wu, *A structural explanation for the low effectiveness of the seasonal influenza H3N2 vaccine*, PLOS PATHOGENS (Oct. 23, 2017), <http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1006682>.

<sup>58</sup> Edward A. Belongia, et al., *Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies*, THE LANCET Volume 16 (Aug. 2016); See also Sarah Zhang, *Scientists Found a Flu Vaccine – Now They Have to Fix It*, WIRED (Oct. 9, 2015), <http://www.wired.com/2015/10/scientists-pinpoint-flu-vaccine-flaw-h3n2/>.

<sup>59</sup> Centers for Disease Control and Prevention, *Interim Estimates of 2017-18 Seasonal Influenza Vaccine Effectiveness – United States, February 2018*, *supra* note 55.

There are many different factors that may contribute to reduced vaccine effectiveness for the influenza, including but not limited to: (1) antigenic differences between the circulating strain and the strain used to create the vaccine caused by antigenic drift and antigenic shift; (2) egg adaptation; and (3) other factors such as immune history<sup>60</sup> and some individuals potentially requiring a higher amount of certain antigens, such as H3N2, to elicit a proper immune response to that particular strain of the influenza. The protective benefit from receiving the flu vaccine typically is decreased if the primary circulating influenza viruses are different from the viruses that were used to make the vaccine for that season.<sup>61</sup> As previously mentioned, influenza viruses are continuously changing through antigenic drift and antigenic shift, and these changes can therefore impact the efficacy of the seasonal flu vaccine if the majority of the circulating viruses become different than those used for the vaccine. Even if antigenic drift occurs, however, the vaccine may provide protective benefit if the circulating influenza virus is only mildly or moderately different than the virus used for the vaccine. If the small genetic changes that occur through antigenic drift accumulate over time and result in a virus that looks different to a person's immune system, the antibodies created against older viruses may no longer recognize the "newer" virus, and the person may no longer be protected.<sup>62</sup>

While vaccine effectiveness is generally interpreted in the context of vaccine match/mismatch to circulating strains that have mutated to explain reduced protection, egg adaptation may also contribute to lower effectiveness of the vaccine—especially for certain strains of the virus such as H3N2.<sup>63</sup> More specifically, as human influenza viruses adapt to grow in eggs during the manufacturing process, genetic changes may occur in the viruses referred to as "egg-adapted changes."<sup>64</sup> These egg-adapted changes can have important consequences for an individual's immune response to vaccination such as causing an individual to produce antibodies that are less effective at preventing illness caused by the specific flu viruses in circulation.<sup>65</sup> In 2014, a study funded by the Canadian Institutes of Health Research found that, during the 2012-2013 flu season, the low vaccine effectiveness was related to mutations in the egg-adapted H3N2 vaccine strain rather than antigenic drift in circulating viruses.<sup>66</sup> Likewise, for the 2017-2018 flu season, some experts have expressed concern that the flu vaccine's reduced effectiveness against

<sup>60</sup> A recent study found that immune history with the influenza influences an individual's response to the flu vaccine. Matt Wood, *Immune history influences effectiveness of flu vaccine, study finds*, UCHICAGONEWS (Feb. 20, 2018), <https://news.uchicago.edu/article/2018/02/20/immune-history-influences-effectiveness-flu-vaccine-study-finds>.

<sup>61</sup> Centers for Disease Control and Prevention, *Flu Vaccine Effectiveness: Questions and Answers for Health Professionals* (last updated Jan. 29, 2016), <https://www.cdc.gov/flu/professionals/vaccination/effectivenessqa.htm>.

<sup>62</sup> Centers for Disease Control and Prevention, *How the Flu Virus Can Change: "Drift" and "Shift,"* (last updated Sept. 27, 2017), <https://www.cdc.gov/flu/about/viruses/change.htm>.

<sup>63</sup> Nicholas C. Wu, *supra* note 58.

<sup>64</sup> Centers for Disease Control and Prevention, *Antigenic Characterization* (last updated Sept. 27, 2017), available at <https://www.cdc.gov/flu/professionals/laboratory/antigenic.htm>.

<sup>65</sup> Centers for Disease Control and Prevention, *Cell-Based Flu Vaccines* (last updated Nov. 7, 2016), <https://www.cdc.gov/flu/protect/vaccine/cell-based.htm>.

<sup>66</sup> Danuta Skowronski, et al., *Low 2012-13 Influenza vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses*, PLOS (Mar. 25, 2014), <http://journals.plos.org/plosone/article?id=10.1371/journal.pone0092153>.

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H3N2 may be caused in part by egg adaptation.<sup>67</sup> According to a February 15, 2018 statement by FDA Commissioner Scott Gottlieb, M.D., the commonly used egg-based manufacturing process may not have produced a vaccine that was as effective against H3N2 as the cell-based manufacturing process:

A preliminary analysis of CMS data indicates that this year, the cell-based influenza vaccine appears to have somewhat better effectiveness in preventing influenza than the egg-based vaccine. Scientists at the FDA, CDC, and NIH are working diligently to fully understand the basis for this finding, so that all of next year's vaccines can provide better protection in preventing the flu. Better understanding why the cell-based vaccine offered better protection against H3N2 this season, when compared to the egg-based vaccine, may offer important clues to help improve the production of a more effective H3N2 vaccine for next season.<sup>68</sup>

Similarly, CDC also recently said "we're hoping this year to find out whether or not there's a performance difference between cell-based vaccines and the egg-based vaccines."<sup>69</sup>

More recently, on February 26, 2018, Dr. Gottlieb indicated that the FDA did not believe that the reduced effectiveness of the 2017-2018 seasonal vaccine against H3N2 was caused by public health authorities choosing the wrong strain of H3N2 when starting the process of making the 2017-2018 seasonal influenza vaccine. Dr. Gottlieb stated that "so far the data we have suggests that the viruses provided by reference laboratories to manufacturers to make this year's vaccines do reasonably match the circulating flu strains that are causing most of the illnesses."<sup>70</sup> Dr. Gottlieb provided several reasons that might explain the limited effectiveness of the 2017-2018 seasonal influenza vaccine against H3N2:

One theory is that people might require a higher amount of H3N2 antigen to elicit a proper immune response to that particular strain of influenza. As I noted previously, the work conducted with CMS shows a preliminary finding that suggests the cell-based influenza vaccine might be somewhat more effective than the egg-based vaccine. We are working to follow up on that finding. We're also combing through the data to see if there are other reasons for why this season's vaccines were less effective against H3N2.<sup>71</sup>

<sup>67</sup> Lisa Schnirring, University of Minnesota, Center for Infectious Disease Research and Policy, *WHO changes 2 strains for 2018-19 flu vaccine* (Feb. 22, 2018), <http://www.cidrap.umn.edu/news-perspective/2018/02/who-changes-2-strains-2018-19-flu-vaccine>.

<sup>68</sup> U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D. on the efficacy of the 2017-2018 influenza vaccine* (Feb. 15, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm597077.htm>.

<sup>69</sup> Maggie Fox, *Why next year's flu vaccine will be lousy, too*, NBC NEWS (Feb. 23, 2018), <https://www.nbcnews.com/health/health-news/why-next-year-s-flu-vaccine-will-be-lousy-too-n850641>.

<sup>70</sup> U.S. Food and Drug Administration, *Statement from FDA Commissioner Scott Gottlieb, M.D., on FDA's ongoing efforts to help improve effectiveness of influenza vaccines* (Feb. 26, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm598317.htm>.

<sup>71</sup> *Id.*

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The FDA anticipates that by better understanding why the effectiveness of the influenza vaccine tends to be lower against H3N2, FDA can hopefully enhance vaccine effectiveness.

### **iii. Vaccine Coverage**

Since 2010, ACIP has recommended annual vaccinations for everyone aged 6 months or older.<sup>72</sup> From the 2010-2011 to 2016-2017 flu seasons, an average of 56.5 percent of children (aged 6 months to 17 years) and 41.7 percent of adults were vaccinated each year.<sup>73</sup> Data from the 2015-2016 season showed that 59.3 percent of children and 41.7 percent of adults were vaccinated.<sup>74</sup> For 2016-2017 season, 59 percent of children and 43.3 percent of adults were vaccinated.<sup>75</sup> The estimate for this season, as of November 2017, was that 38.6 percent of all persons 6 months and older received the flu vaccine (this early estimate of flu season vaccination coverage is similar to coverage at the same time last flu season for all persons 6 months and older).<sup>76</sup>

The Department of Health and Human Services (HHS) supports efforts to increase annual vaccination and continuously engages in efforts to improve public awareness and provider knowledge about influenza and the importance of vaccination.<sup>77</sup> As part of the Healthy People 2020 initiative, HHS has set a goal for states to vaccinate 70 percent of their population. According to experts, vaccination rates need to be generally above 70 percent for “herd immunity” effects—which limit the spread and protect those without immunity—to become apparent.

### **D. Development of a Universal Flu Vaccine**

One long-term goal to improve preparedness for and response to the influenza is to develop a universal vaccine that would provide long-lasting immunity against multiple strains of the influenza. The goal is to eliminate the need for individuals to receive an annual seasonal flu vaccine and to provide protection against newly emerging flu strains. The Biomedical Advanced Research and Development Authority (BARDA) within the Office of the Assistant Secretary for Preparedness and Response in the U.S. Department of Health and Human Services is coordinating a broad-interagency partnership to support the development of improved influenza vaccines, including a universal flu vaccine.<sup>78</sup> In June 2017, the National Institute of Allergy and Infectious Disease (NIAID) held a workshop entitled “Pathway to a Universal Influenza Vaccine” to identify and develop criteria that would define a universal influenza vaccine, discuss knowledge gaps in the search for this vaccine, and to identify research strategies to address these

<sup>72</sup> Centers for Disease Control and Prevention, *FY 2018 Congressional Budget Justification*, *supra* note 3, at 18.

<sup>73</sup> Centers for Disease Control and Prevention, *Flu Vaccination Coverage, United States, 2016-17 Influenza Season* (last updated Sept. 28, 2017), <https://www.cdc.gov/flu/fluview/coverage-1617estimates.htm>.

<sup>74</sup> *Id.*

<sup>75</sup> *Id.*

<sup>76</sup> Centers for Disease Control and Prevention, *National Early-Season Flu Vaccination Coverage, United States, November 2017* (last updated Dec. 9, 2016), <https://www.cdc.gov/flu/fluview/nifs-estimates-nov2017.htm>.

<sup>77</sup> Centers for Disease Control and Prevention, *FY 2018 Congressional Budget Justification*, *supra* note 3, at 46.

<sup>78</sup> Centers for Disease Control and Prevention, *Influenza Vaccine Advances—Questions and Answers* (last updated Sept. 28, 2016), <https://www.cdc.gov/flu/about/qa/advances.htm>.

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gaps.<sup>79</sup> Following the workshop, NIAID published a strategic plan in February 2018 to “reinvigorate pursuit of a universal influenza vaccine.”<sup>80</sup>

### E. Pandemic Influenza

An influenza pandemic can occur when a novel, non-human influenza virus becomes able to spread efficiently through human-to-human transmission. The viruses circulate in birds or other animals, so there is little to no immunity against these viruses among people. According to CDC, pandemics rarely occur and past pandemics include the 2009 Pandemic (H1N1 virus), the 1968 Pandemic (H3N2 virus), the 1957-1958 Pandemic (H2N2 virus), and the 1918 Pandemic (H1N1 virus).<sup>81</sup>

HHS maintains a *Pandemic Influenza Plan* that was developed in 2005.<sup>82</sup> The Committee wrote to HHS in April 2017 asking about the status of the updated plan.<sup>83</sup> HHS subsequently released the updated plan in June 2017.<sup>84</sup> The *Pandemic Influenza Plan* acts “as a blueprint for all HHS pandemic influenza preparedness planning and response activities.”<sup>85</sup> In the 2017 update, HHS notes that one of the improvements in the agency’s preparedness and response activities for pandemic influenza over the past decade is that “HHS efforts in pandemic influenza preparedness now are closely aligned with seasonal influenza activities, harnessing expanded surveillance, laboratory, vaccine, and antiviral drug resistance monitoring capacity.”<sup>86</sup> According to the 2017 update:

[T]he continually changing nature of influenza viruses that can lead to mismatches between vaccine strains and circulating viruses, as seen during the 2014-2015 influenza season, remind us that pandemic and seasonal influenza planning and improvement efforts are interdependent. Both rely on a strong and sustainable public health system infrastructure that can rapidly detect, and respond to, changes in circulating influenza viruses. Many of the activities that HHS and its partners

<sup>79</sup> National Institutes of Health, National Institute of Allergy and Infectious Disease, *Experts Outline Pathway to a Universal Influenza Vaccine* (Oct. 17, 2017), <https://www.niaid.nih.gov/news-events/experts-outline-pathway-universal-influenza-vaccine>.

<sup>80</sup> Emily J. Erbeling, et al., *A Universal Influenza Vaccine: The Strategic Plan for the National Institute of Allergy and Infectious Diseases* (Mar. 2018).

<sup>81</sup> Centers for Disease Control and Prevention, *Past Pandemics* (last updated Nov. 2, 2017), <https://www.cdc.gov/flu/pandemic-resources/basics/past-pandemics.html>.

<sup>82</sup> Centers for Disease Control and Prevention, *National Pandemic Influenza Plans* (last updated Jun. 22, 2017), <https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/national-strategy-planning.html>.

<sup>83</sup> Letter from the Hon. Greg Walden, Chairman, H. Comm. on Energy & Commerce, et al., to Hon. Thomas Price, M.D., Sec’y, U.S. Dep’t of Health & Human Services (Apr. 20, 2017), <https://archives-energycommerce.house.gov/sites/republicans.energycommerce.house.gov/files/documents/20170420HHS.pdf>. In response to Questions for the Record from the Subcommittee’s November 2015 hearing on seasonal influenza, HHS told the Committee that it expected to release the updated plan by the end of 2016. *Id.*

<sup>84</sup> Centers for Disease Control and Prevention, *National Pandemic Influenza Plans* (last updated Jun. 22, 2017), <https://www.cdc.gov/flu/pandemic-resources/planning-preparedness/national-strategy-planning.html>.

<sup>85</sup> U.S. Dep’t of Health & Human Serv., *HHS Pandemic Influenza Plan*, at 2 (Nov. 2005), <http://www.flu.gov/planning-preparedness/federal/hhs/pandemicinfluenzaplan.pdf>.

<sup>86</sup> U.S. Dep’t of Health and Human Services, *Pandemic Influenza Plan, 2017 Update* (Jun. 2017), <https://www.cdc.gov/flu/pandemic-resources/pdf/pan-flu-report-2017v2.pdf>.

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undertake each year to understand and mitigate the impact of seasonal influenza are critical to a pandemic response both domestically and globally.<sup>87</sup>

#### **F. Improvements in U.S. Response to Seasonal Influenza**

After the 2014-2015 vaccine mismatch, then HHS Secretary Sylvia Burwell, through her counselors, requested that HHS experts recommend actions to mitigate the seasonal influenza mismatch problem. On May 6, 2015, a memorandum of influenza process improvements was sent to Secretary Burwell. In November 2015, HHS held a table top exercise with HHS agencies and vaccine manufacturers, to solicit their individual opinions. The exercise outcome is expected to inform an HHS action plan for rapid development and manufacturing of a revised seasonal influenza vaccine as a strain change or a separate monovalent vaccine. On November 19, 2015, the Subcommittee held a hearing on whether the public health response to seasonal influenza had improved.<sup>88</sup> The Subcommittee will follow-up on the status of HHS actions.

Among the key actions taken to improve seasonal flu preparedness and examined at the hearing were:

- *Technological improvements.* Vaccine manufacturers were in the process of adopting several process improvements for pandemic vaccine. HHS anticipated asking that these improvements also be applied to seasonal influenza vaccine manufacturing. Application of these improvements to seasonal influenza could save four to six weeks in the manufacturing and formulation process. If successful, strain selection decisions could be made with surveillance information closer to the beginning of the influenza season.
- *Use of the Influenza Risk Assessment Tool (IRAT).* HHS uses the IRAT for decisions to make limited amounts of vaccine in response to emerging, potentially-pandemic strains. The HHS Influenza Risk Management Group, using the IRAT as a model, was working to develop a risk assessment method within the next 15 months to guide recommendations about whether to change seasonal vaccine strain composition between the WHO recommendation and June.
- *Monovalent rescue vaccine.* Recent discussions at the Flu Risk Management Meeting (FRMM), which is coordinated by the HHS Office of the Assistant Secretary for Preparedness and Response (ASPR), have included considerations to determine that circumstances under which a monovalent rescue vaccine would be pursued due to a drifted seasonal influenza strain. Factors that could impact that decision include manufacturing capabilities and disease severity. In 1986, FDA approved a monovalent influenza vaccine to supplement the trivalent influenza vaccine to address

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<sup>87</sup> *Id.* at 10.

<sup>88</sup> Hearing before the U.S. House of Reps., Energy and Commerce Subcommittee on Oversight and Investigations, “U.S. Public Health Preparedness for Seasonal Influenza: Has the Response Improved?” (Nov. 19, 2015).

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a drift of the H1N1 strain.<sup>89</sup> Approximately 7 million doses of the 1986 monovalent vaccine were manufactured or distributed late in 1986.<sup>90</sup>

- *Late season change to tri- or quadrivalent vaccine.* HHS had taken a series of steps to increase the probability that a late season change to tri- or quadrivalent vaccine could be made. These changes would also enable faster production of a monovalent vaccine should it be needed. Some of these key steps include: FDA making more potency assay reagents to facilitate the production of new vaccines, CDC (with WHO) helping improve availability of additional vaccine viruses, CDC (with WHO) enhancing global surveillance of circulating human and avian influenza viruses.
- *Increased communication.* More frequent and comprehensive communication with HHS leadership and FDA had been implemented, and FDA had done likewise with the Chair of its Vaccines and Related Biological Products Advisory.

#### IV. Issues

The following issues may be examined at the hearing:

- How has public health preparedness for the seasonal influenza improved in recent years?
- What challenges do public health authorities face when developing the seasonal influenza vaccine?
- How can better and more effective influenza vaccines be manufactured? Are there concerns with the egg-based manufacturing process?
- What guidance would be effective in helping increase the use of antiviral medications and reduce the use of antibiotics in the treatment for influenza? Do we need more treatments for the flu?

#### V. Staff Contacts

If you have any questions regarding the hearing, please contact Natalie Turner, Alan Slobodin, or Jen Barblan of the Committee staff at (202) 225-2927.

<sup>89</sup> Letter from Thomas A. Kraus, FDA Associate Commissioner for Legislation to The Honorable Fred Upton, Chairman, House Energy and Commerce Committee, et al. (April 8, 2015).

<sup>90</sup> Centers for Disease Control and Prevention, 37 CDC Morbidity and Mortality Weekly Report 469 (Aug. 12, 1988).



GREG WALDEN, OREGON  
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March 28, 2018

Dr. Anne Schuchat  
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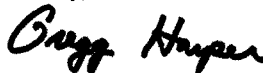
Dear Dr. Schuchat:

Thank you for appearing before the Subcommittee on Oversight and Investigations on March 8, 2018, to testify at the hearing entitled "Examining U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza."

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday April 11, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to [Ali.Fulling@mail.house.gov](mailto:Ali.Fulling@mail.house.gov).

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Gregg Harper  
Chairman  
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment

Schuchat March 2018 Hearing QFRS:

**Rep. Harper**

**Q1. What specific steps is CDC taking to examine whether the different manufacturing processes (i.e. cell-based, recombinant-based, and egg-based) for the flu vaccine have an impact on the flu vaccine effectiveness? What additional data do we need to make this comparison?**

A1.

CDC supports the U.S. Flu Vaccine Effectiveness (VE) Network, which currently consists of five study sites across the United States that measure flu vaccines' effectiveness at preventing outpatient medical visits due to laboratory-confirmed influenza. The VE network allows CDC to measure the benefits of seasonal flu vaccination each flu season. CDC plans to work with existing network partners next year to conduct some limited additional studies to assess the relative effectiveness of different vaccine products. In the past similar such studies have successfully compared live attenuated vaccine vs inactivated vaccine in children, quadravalent (four components that protect against four flu viruses) and trivalent vaccines (three components), and high dose vaccines to standard dose vaccines.

In order to better evaluate the impact of different manufacturing processes on VE on a broader and more consistent scale, CDC would need to expand the VE network, such as by adding enrollees to existing outpatient VE network sites and increasing the number of study sites. These findings will provide additional important information to researchers and manufacturers working to develop more effective vaccines. By increasing the breadth and depth of vaccine effectiveness monitoring to gather additional comparative effectiveness data in support of the development of more effective vaccines, CDC would be able to generate evidence that could affect future policy.

**Q2. A high-dose vaccine has been available for several years, but CDC's Advisory Committee on Immunization Practices (ACIP) has not expressed a preference for the high-dose vaccine for seniors. During the March 8, 2018 hearing, Dr. Schuchat testified that one reason CDC has not expressed a preference is because: "the vaccine that they have at the doctors' office or the pharmacy is the one that you should get because there may not be the other product if you're looking for it." Is this the main reason the CDC and ACIP have not expressed a preference for the high-dose flu vaccine in seniors? If not, why haven't CDC and ACIP expressed a preference that the elderly receive the high-dose flu vaccine? What data is needed to get CDC to the point of expressing a preference for the high-dose vaccine for seniors? Since there are several studies that show a high-dose vaccine is about 20 percent more effective than the standard-dose vaccine in seniors, how does the CDC's no preference posture save more lives than would be saved by expressing a preference for the high-dose vaccine for seniors?**

A2.

There are several reasons why a preferential recommendation is not currently in place. Where more than one vaccine exists for a given disease, preferential recommendations for one vaccine over another generally require strong, generalizable evidence of superior effectiveness. Influenza is unique in that vaccine effectiveness varies with a number of different factors, and is not the same from one season to another. In recent years, studies have been conducted comparing the benefits for older adults of high-dose inactivated influenza vaccine, adjuvanted inactivated influenza vaccine, and recombinant influenza vaccine to standard-dose, unadjuvanted influenza vaccines. For each of these three vaccines, there is at least some evidence of better effectiveness than standard-dose inactivated vaccine, with the most evidence available for the high dose vaccine. To date, however, there are no data comparing the effectiveness of these three vaccines to one another, and so it is not

possible to draw conclusions as to which is the most effective. Moreover, it is not possible to know whether the findings of such studies, which are generally performed over only one or two seasons, will be similar across multiple influenza seasons. For example, in one two-season study comparing high-dose and standard-dose vaccines, improved efficacy of the high dose vaccine was seen only during one season. In addition, preferential recommendations may discourage vaccination in settings where it is difficult to find a specific vaccine type. ACIP routinely reviews vaccine data from manufacturers and academic researchers, and will continue to review information on this topic as it becomes available. CDC continues to gather and compile data on this topic to inform ACIP recommendations.

**Q3. During the March, 2018 hearing, CDC testified that about 48% of Americans get the flu vaccine each year. More children than adults typically get vaccinated, with about 59 percent of children typically receiving the flu vaccine.**

**a. Do all pediatrician offices carry pediatric doses of the flu vaccine for the entire flu season?**

CDC monitors vaccine distribution data nationally and estimates that more than 154 million doses of flu vaccine have been shipped nationwide. CDC also purchases and distributes influenza vaccine for the public sector and, on a monthly basis, provides state health departments with an updated status on public doses ordered for providers. CDC, however, does not track the individual vaccine usage at the provider level.

In the private sector, there are two tools to support influenza vaccination for providers and the public. First, anyone can use the Flu Vaccine Finder on CDC's website (<https://www.cdc.gov/flu/freeresources/flu-finder-widget.html>) to find providers of flu vaccine based on geographic location. Second, the National Adult and Influenza Immunization Summit hosts the Influenza Vaccine Tracking Availability System, a resource for providers looking to purchase influenza vaccine.

**b. Do all pharmacies carry pediatric doses of the flu vaccine throughout the entire flu season?**

CDC does not have direct visibility into vaccine supply of private sector pharmacies as our focus is on the public sector through connection with state, city, and territorial health departments. Again, anyone can use the Flu Vaccine Finder on CDC's website (<https://www.cdc.gov/flu/freeresources/flu-finder-widget.html>) to find providers of flu vaccine based on geographic location.

**c. Is CDC aware of any difficulties parents have encountered when trying to have their child get the flu vaccine?**

CDC is not aware of any difficulties that parents may have encountered when trying to have their child immunized with the flu vaccine. CDC works closely with immunization programs at all state health departments and our awardees did not communicate any difficulties regarding vaccine availability for children; however, as stated above, there are additional options available for CDC immunization awardees to obtain additional influenza vaccine, if needed.

**Q4. The Advisory Committee on Immunization Practice (ACIP) recently recommended that FluMist be used during the 2018-2019 season. Why did the advisory panel decide to recommend FluMist for the 2018-2019 season?**

In 2016, based on CDC data from the 2013-14 and 2015-16 seasons, the ACIP recommended that live attenuated inactivated virus (LAIV), or FluMist, not be used due to concerns over poor effectiveness against influenza A H1N1 viruses. During the February 2018 ACIP meeting, information presented to the Committee that indicated that the probable cause of poor effectiveness of a certain component of the vaccine had been identified. The manufacturer has updated this vaccine component, and data suggest that the problem may have been addressed with this change. The effectiveness of the LAIV containing the new component may not be known until the next H1N1-predominant influenza season occurs. It will thus continue to be important for CDC to monitor influenza vaccine effectiveness.

**Q5. Has there been any analysis of whether insurance reimbursement policies and other practices impacts the rate of vaccination or spread of influenza? Do insurance reimbursement policies differ depending on whether the vaccine was manufactured through egg-based process, cell-based process, or recombinant-based process?**

A5. All flu vaccines are covered by insurance since they are recommended by the Advisory Committee on Immunization Practices (ACIP). CDC is unaware of any difference in reimbursement policies based on which process was used to manufacture the flu vaccine.

**Rep. Carter:**

**Q1. This is the 100<sup>th</sup> anniversary of the 1918 pandemic influenza that infected about 500 million people worldwide, killing 20 to 50 million. Since then, we have made significant improvements in technologies to treat and prevent flu, but a pandemic flu is still a real threat. Can you discuss our level of preparedness as a country and what more could be done to better equip our public health infrastructure to respond to an outbreak of influenza?**

A1.

CDC and its public health partners must continue to be vigilant and prepare for the emergence of the next influenza pandemic, while working to minimize the burden of seasonal influenza, which causes significant disease burden in the U.S. each year. CDC's seasonal and pandemic prevention and response work is synergistic. Better preparedness and response for seasonal influenza results in better pandemic preparedness and vice versa.

CDC has made significant progress and improvements in methods and technologies to diagnose, treat, and prevent influenza, but because of the dynamic and evolving nature of flu viruses, a future flu pandemic is inevitable. Developments since the 1918 influenza pandemic include major advances in medicine, technology, and public health. We now have vaccines to prevent flu, antiviral drugs (which are the main treatment for flu), and a global influenza surveillance system with 114 World Health Organization member states that constantly monitor flu activity. In addition, CDC is one of six WHO Influenza Collaborating Centers that conduct research and convene vaccine composition meetings twice a year to make recommendations on viruses to be included in seasonal, as well as pre-pandemic, influenza vaccines. There is also a much better understanding of the use of non-pharmaceutical interventions that help slow the spread of flu, such as social distancing, respiratory and cough etiquette and hand hygiene. These advances in pandemic preparedness and response are critical, but there is still much to do to improve pandemic readiness. CDC tracks influenza virus activity in the US with strong

epidemiologic and virologic surveillance systems and has made great progress developing global capacity to detect novel influenza when it emerges.

Despite these advances, surveillance and laboratory infrastructure is lacking in many developing countries. Assisting countries to develop such surveillance capacity, and to create and exercise robust pandemic plans will mitigate pandemic impact on Americans, as will improving surveillance of flu viruses in animals. In addition, more broadly effective tools to prevent and treat flu (i.e. vaccine and antivirals) are needed, as well as surge capacity strategies for medical settings, supplies, and personnel. The 1918 pandemic centenary gives us an opportunity to explore the historic impact of this event and also reminds us that influenza is unpredictable and has the potential to cause devastating harm. CDC is committed to protecting Americans and the global community by preparing for and responding to future flu pandemics. An effective response will save lives and diminish the potential for social and economic turmoil.

GREG WALDEN, OREGON  
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY  
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS  
**Congress of the United States**  
**House of Representatives**  
COMMITTEE ON ENERGY AND COMMERCE  
2125 RAYBURN HOUSE OFFICE BUILDING  
WASHINGTON, DC 20515-6115  
Majority (202) 225-2927  
Minority (202) 225-3841  
March 28, 2018

Dr. Anthony S. Fauci  
Director, National Institute of Allergy and Infectious Diseases  
National Institutes of Health  
U.S. Department of Health and Human Services  
9000 Rockville Pike  
Bethesda, MD 20892

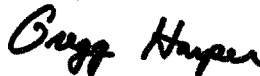
Dear Dr. Fauci:

Thank you for appearing before the Subcommittee on Oversight and Investigations on March 8, 2018, to testify at the hearing entitled "Examining U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza."

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday April 11, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to [Ali.Fulling@mail.house.gov](mailto:Ali.Fulling@mail.house.gov).

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Gregg Harper  
Chairman  
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment

**Committee on Energy and Commerce**  
**Subcommittee on Oversight and Investigations**  
**Hearing: "Examining U.S. Public Health Preparedness for and Response Efforts to**  
**Seasonal Influenza"**  
**March 8, 2018**

**Questions for the Record for Dr. Anthony S. Fauci, Director,**  
**National Institute of Allergy and Infectious Diseases, National Institutes of Health**

**The Honorable Gregg Harper**

1. What specific steps is NIH taking to examine whether the different manufacturing processes (*i.e.*, cell-based, recombinant-based, and egg-based) for the flu vaccine have an impact on the flu vaccine's effectiveness? What additional data do we need to make this comparison?

NIH Response:

The National Institute of Allergy and Infectious Diseases (NIAID), a component of the National Institutes of Health (NIH), maintains a robust influenza research program that includes efforts to improve upon existing seasonal influenza vaccines. A key goal of the recently released *NIAID Strategic Plan for the Development of a Universal Influenza Vaccine* is to precisely characterize how the development of immunity to influenza virus occurs and how best to tailor vaccination responses to achieve it. These NIAID efforts will include supporting the development and study of different vaccine candidate designs that may utilize novel manufacturing processes.

Each year, the Centers for Disease Control and Prevention collects data about seasonal influenza vaccination via the U.S. Flu Vaccine Effectiveness (VE) Network. The VE Network helps estimate the influenza vaccine's effectiveness at preventing outpatient medical visits due to laboratory-confirmed influenza. Though NIAID is not part of the VE Network and cannot comment on its data needs, NIAID does support research to better understand how different manufacturing processes may have an impact on the effectiveness of various influenza vaccine formulations. This research can help to understand why a particular vaccine may be more or less effective, as determined by the VE Network, during a particular influenza season. For example, NIAID-supported investigators recently determined that an influenza vaccine virus produced in eggs exhibited a mutation that may have resulted in reduced vaccine effectiveness during the 2016-2017 influenza season. This study also showed that a recombinant-based influenza vaccine approved for use during the 2016-2017 influenza season did not exhibit this mutation and elicited a more robust immune response in vaccine recipients.

NIAID also is supporting research to help avoid challenges associated with egg-based production of influenza vaccines, such as the egg-specific mutation described above. This research includes studies to improve current manufacturing processes and to develop novel influenza vaccine production approaches. For example, NIAID scientists have devised a method to manufacture an experimental whole virus inactivated influenza vaccine using a cell-based system, rather than eggs. This would provide another alternative to currently licensed egg-based and cell-based

influenza vaccines. NIAID researchers are developing an additional cell-based system for whole virus influenza vaccine candidates to try to determine which system is more efficient (both in terms of manufacturing time and cost). NIAID will continue to support efforts to improve vaccine manufacturing processes and vaccine efficacy. Data from these NIAID-supported studies will help inform the design of better influenza vaccines.

It is important to note that the ability of an influenza vaccine to elicit an immune response may be affected by factors that are not associated with the vaccine virus or the manufacturing process. For example, a recent NIAID-supported study found that the low vaccine effectiveness observed during the 2012-2013 influenza season was attributed to low immunogenicity in a subset of the population, not to viral mutations acquired during the manufacturing process. NIAID continues to support fundamental immunological research to better understand the immune response to influenza vaccination. This work includes studies exploring why some individuals respond poorly to influenza vaccines, as well as how influenza exposures and vaccinations shape an individual's immune response.

2. Adjuvants are boosters that can be used in flu vaccine to enhance the immune response in certain populations that tend to respond poorly to vaccination, such as the elderly. Seasonal flu vaccines are administered with adjuvants licensed for use in other countries for targeted populations, such as the elderly. Adjuvants have been used in other vaccines licensed for the U.S. market-such as in vaccines against tetanus. What further research is needed about the use of adjuvants in the seasonal flu vaccine?

NIH Response:

NIAID maintains a strong vaccine adjuvant program that supports the discovery and development of novel adjuvants capable of safely enhancing the efficacy of seasonal, pandemic, and universal influenza vaccines in various populations including the elderly, newborns and infants, and pregnant women. NIAID-supported investigators have tested several promising experimental adjuvants for influenza vaccines that have induced protection against influenza infection in animal models. A number of these adjuvant-vaccine combinations also are being tested in early stage clinical trials.

In collaboration with industry partners, including small businesses, NIAID continues to support research to evaluate novel adjuvants with licensed seasonal influenza vaccines to enhance vaccine effectiveness. In addition, NIAID is developing a clinical trial to evaluate the use of a topical adjuvant cream to boost immune responses to an H5 influenza vaccine. This topical adjuvant cream has shown promise in boosting immune responses to seasonal influenza vaccines. NIAID also collaborates with the Biomedical Advanced Research and Development Authority (BARDA) and industry partners to evaluate adjuvants to improve immune responses to avian H5 and H7 influenza vaccines and to enable dose-sparing regimens of these vaccines.

NIAID will continue to support research to understand how adjuvants augment immune responses. This research is critical to the goal of enhancing influenza vaccine effectiveness, particularly in individuals that respond poorly to seasonal influenza vaccination.



3. What actions could Congress take that could help expedite research for the universal flu vaccine?

NIH Response:

NIAID is appreciative of Congress' longstanding support for influenza virus research. Through activities such as public hearings, Congress continues to play an essential role in raising awareness of the need for a universal influenza vaccine. In addition, Congress, through the passage of the Consolidated Appropriations Act, 2018 (P.L. 115-141), provided an additional \$40 million to NIAID for universal influenza vaccine research that will expedite studies of: 1) transmission, natural history, and pathogenesis of influenza infection; 2) influenza immunity and factors correlated with immune protection; and 3) vaccine approaches to elicit broad, protective immune responses. Additional sustained financial resources will be required to develop such an important advance in the fight against influenza.

**The Honorable Earl "Buddy" Carter**

1. I am aware of a great deal of ongoing work on the next generation of flu vaccines. This includes in my home state of Georgia where there is a partnership between the University of Georgia and Sanofi to develop a broadly protective flu vaccine that would be effective against influenza natural mutation over time. Can you talk about the role of the NIH in supporting early stage research and the importance of public/private partnerships in the development of next-generation flu vaccines?

NIH Response:

Early stage research, from basic research to applied research and preclinical and early clinical studies, is an essential component of the NIH's mission and a critical part of the development of new tools to treat and prevent disease. For example, a recent analysis found that out of the 210 new drugs approved by the Food and Drug Administration from 2010 through 2016, NIH contributed to every single one. In more than 90 percent of these cases, the NIH-supported research was early stage science that provided foundational information for development of the drug. In a recent influenza-related case, it was an NIAID investment in basic research nearly 40 years ago that enabled the development of the novel influenza antiviral Xofluza (baloxavir marboxil), which was approved for use in Japan in early 2018.

Support for early stage research also creates tremendous opportunities for NIAID to work with public and private partners to translate basic scientific findings into interventions for patients. NIAID's Partnerships Program, which encourages new research collaborations between experts from academia and industry, has stimulated research and development of vaccines with broad activity against a range of influenza viruses. NIAID also participates in interagency public-private partnerships with agencies such as BARDA and supports databases such as the Immune Epitope Database and ImmPort, which facilitate the broader research community's influenza vaccine development efforts. NIAID will continue to collaborate with government, academic, and industry partners to develop the next generation of vaccines against influenza.

GREG WALDEN, OREGON  
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY  
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS  
**Congress of the United States**  
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WASHINGTON, DC 20515-6115  
Majority (202) 225-2827  
Minority (202) 225-3641  
March 28, 2018

Dr. Rick A. Bright  
Director, Biomedical Advanced Research and Development Authority  
Deputy Assistant Secretary, Office of the Assistant Secretary for Preparedness and Response  
U.S. Department of Health and Human Services  
200 Independence Avenue, S.W.  
Washington, DC 20201

Dear Dr. Bright:

Thank you for appearing before the Subcommittee on Oversight and Investigations on March 8, 2018, to testify at the hearing entitled "Examining U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza."

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday April 11, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to [Ali.Fulling@mail.house.gov](mailto:Ali.Fulling@mail.house.gov).

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Gregg Harper  
Chairman  
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment

[Dr. Bright did not answer submitted questions for the record by the time of printing.]

Attachment—Additional Questions for the Record

The Honorable Gregg Harper

1. Some studies have shown that the cell-based and recombinant-based flu vaccines are more effective than the egg-based flu vaccine. One challenge, however, in comparing the effectiveness of flu vaccines manufactured through different processes is that the vaccine is blended together in the market and we therefore do not have differentiated data sets to show the benefit and effectiveness of egg-based or non-egg-based vaccines.
  - a. What, if any, data is available to evaluate whether vaccines manufactured through different technologies are more effective? Is all the available data being analyzed?
  - b. What additional data do we need and how can this data be obtained?
2. During the March 8, 2018 hearing, BARDA testified that we have not had a new class of antivirals approved for influenza in more than 20 years. What, if anything, should we be doing to incentivize the development of new antivirals for the flu?
3. On November 19, 2015, the Subcommittee held a hearing on HHS actions being taken to improve the public health response to influenza. In 2015, HHS reported that it would ask vaccine manufacturers that were adopting process improvements for a pandemic vaccine to also apply such improvements to seasonal influenza vaccine manufacturing. Did HHS make such a request to the manufacturers? If so, have these process improvements been adopted for seasonal influenza vaccine manufacturing?
4. Does BARDA have the resources needed to keep the vaccines in the stockpile updated? Are we transitioning to cell-based or recombinant flu vaccines in the stockpile? If so, at what rate?

The Honorable Morgan Griffith

1. In 2011, FDA issued an Advisory to alert drug manufacturing to the presence of glass fragments in injectable drugs contained in glass vials. Industry experts inform me that this phenomenon is due the delamination of glass from the inner surface of the vial. This problem has led to many recalls because FDA believes that these glass fragments have the potential to cause harm to patients. I know that BARDA, CDC, FDA and NIH work tirelessly to ensure our influenza vaccine stockpile is safe and secure, but:
  - a. Have you seen any evidence of glass fragments due to delamination or evidence of glass particles in influenza vaccines contained in glass vials after the vaccines are manufactured and included within the national vaccine stockpile?
  - b. If you have seen such evidence, what can be done to address the problem?

GREG WALDEN, OREGON  
CHAIRMAN

FRANK PALLONE, JR., NEW JERSEY  
RANKING MEMBER

ONE HUNDRED FIFTEENTH CONGRESS  
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WASHINGTON, DC 20515-6115  
Majority (202) 225-2927  
Minority (202) 225-3641  
March 28, 2018

The Honorable Scott Gottlieb, MD  
Commissioner  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Silver Spring, MD 20993

Dear Dr. Gottlieb:

Thank you for appearing before the Subcommittee on Oversight and Investigations on March 8, 2018, to testify at the hearing entitled "Examining U.S. Public Health Preparedness for and Response Efforts to Seasonal Influenza."

To facilitate the printing of the hearing record, please respond to these questions with a transmittal letter by the close of business on Wednesday, April 11, 2018. Your responses should be mailed to Ali Fulling, Legislative Clerk, Committee on Energy and Commerce, 2125 Rayburn House Office Building, Washington, DC 20515 and e-mailed in Word format to [Ali.Fulling@mail.house.gov](mailto:Ali.Fulling@mail.house.gov).

Thank you again for your time and effort preparing and delivering testimony before the Subcommittee.

Sincerely,



Gregg Harper  
Chairman  
Subcommittee on Oversight and Investigations

cc: The Honorable Diana DeGette, Ranking Member, Subcommittee on Oversight and Investigations

Attachment



JUL 23 2018

The Honorable Gregg Harper  
Chairman  
Subcommittee on Oversight and Investigations  
Committee on Energy and Commerce  
U.S. House of Representatives  
Washington, D.C. 20515

Dear Chairman Harper:

Thank you for providing the Food and Drug Administration (FDA or the Agency) with the opportunity to testify at the March 8, 2018, hearing before the Committee on Energy and Commerce, Subcommittee on Oversight and Investigations, entitled "Examining U. S. Public Health Preparedness for and Response Efforts to Seasonal Influenza." This letter is a response for the record to questions posed by the committee.

If you have further questions, please let us know.

Sincerely,



John Martin  
Principal Associate Commissioner  
for Legislative Affairs

Your questions are restated below in bold, followed by FDA's response.

**The Honorable Gregg Harper**

1. **During the March 8, 2018 hearing, FDA indicated that in some years we have observed better efficacy with the egg-based vaccine than the cell-based process. What years have we seen more efficacy with the egg-based vaccine and what was the basis for this finding?**

The cell-based influenza vaccine was first approved for use on November 20, 2012. Based on the best scientific information available, it is believed that the efficacy of the egg-based and cell-based vaccines could vary in relationship to one another depending on the circulating influenza strains or other factors related to the production process. However, because the cell-based vaccine has been more widely administered over only the past few years, robust data regarding its efficacy versus the egg-based vaccine prior to the 2017-2018 season are not available.

2. **While the flu vaccine helps prevent individuals from getting the flu and may even reduce the severity of the illness in those individuals that do get the flu, there is always room for improvement. This year the vaccine had a reduced level of effectiveness, especially in certain age groups and against the deadliest strain of the flu virus, H3N2. On February 15, 2018, FDA issued a statement indicating that "a preliminary analysis of CMS data indicates that this year, the cell-based influenza vaccine appears to have somewhat better effectiveness in preventing influenza than the egg-based vaccine"<sup>1</sup> and that "scientists at the FDA, CDC, and NIH are working diligently to fully understand the basis for this finding."<sup>2</sup>**

- a. **When did FDA have reason to believe that the cell-based manufacturing process for the flu vaccine might have better effectiveness than the egg-based manufacturing process?**

As you may know, no other routine vaccine is produced, FDA-approved, and distributed every year across the United States within an approximately six-month time frame. Vaccine manufacturers annually submit to FDA a supplement to their license to include the updated influenza virus antigens in their vaccine. FDA must review and approve a supplement before the updated version of the influenza vaccine containing new virus antigens can be distributed. Manufacturing of each antigen to be included in the vaccines occurs sequentially over several months, usually from December (produced at risk by manufacturers before the strain recommendations are made) until late May. In parallel with vaccine manufacturing, FDA develops and calibrates reagents that are provided to the vaccine manufacturers and our regulatory counterparts throughout the world.

<sup>1</sup> U.S. Food and Drug Administration, Statement from FDA Commissioner Scott Gottlieb, M.D., on the efficacy of the 2017-2018 influenza vaccine (Feb. 15, 2018; updated Feb. 16, 2018), <https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm597077.htm>.

<sup>2</sup> *Id.*

Typically, FDA approves the updated seasonal influenza vaccines with new labeling by the end of July.

For the 2017-2018 influenza season, FDA's Vaccines and Related Biological Products Advisory Committee (VRBPAC) met on March 9, 2017, to provide recommendations on the composition of the influenza vaccine. During this meeting, VRBPAC reviewed and evaluated the surveillance data related to epidemiology and antigenic characteristics of recent influenza isolates, serological responses to 2016-2017 vaccines, and the availability of candidate strains and reagents. By January of 2018, it was clear that the influenza season was severe, and that H3N2 was the predominant circulating strain. Based on preliminary reports from the Southern Hemisphere 2017 influenza season that indicated lower than desirable effectiveness of the influenza vaccine against H3N2, the FDA Center for Biologics Evaluation and Research (CBER) collaborated with the Centers for Medicare & Medicaid Services (CMS) to examine relative vaccine effectiveness compared to egg based inactivated vaccines. This work was initiated in late January 2018, and by mid-February, preliminary results were available indicating that the cell-based vaccine was about 20 percent more effective relative to the egg-based standard-dose quadrivalent and trivalent influenza vaccines.

**b. How much more effective is the cell-based influenza vaccine than the egg-based vaccine according to the preliminary data?**

FDA and CMS used data on Medicare beneficiaries ages  $\geq 65$  years who received an egg-based or cell-cultured influenza vaccination from August 6, 2017 through January 4, 2018 to estimate the relative effectiveness of the influenza vaccines as measured by hospitalization or emergency room visits for influenza. Among this group, the data available as of March 2018 suggested that the cell-based vaccine was about 20 percent more effective relative to the egg-based standard-dose quadrivalent and trivalent influenza vaccines in this population.

**c. Does FDA believe that egg-adaptation was a possible factor in the reduced effectiveness of the vaccine this year?**

Yes. The data presented by CDC at FDA's March 1, 2018, VRBPAC meeting, and discussed in the June 8, 2018 MMWR, indicates that egg adaptation may have contributed to the reduced effectiveness of the 2017-2018 seasonal influenza egg-based vaccine. Egg adaptation is the process by which a candidate virus is passaged through eggs in order to optimize its production yield.